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ON ACETIC ACID AS A SUBSTITUTE FOR ETHYL ALCOHOL IN EXTRACTING THE ACTIVE PRINCIPLES OF SOME OFFICINAL DRUGS.

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(SECOND PAPER.)

In continuing this subject for a second paper the writer refers to, without repeating, the introductory matter of the first paper, where the therapeutic and pharmaceutic bearings of such a substitution are discussed and passes at once to the farther work which is relied upon to support or oppose the proposed substitution and define the limits of its application.

In the meantime, it may be well to state that the guarded use of extracts and fluid extracts made with acetic acid has continued and extended in veterinary therapeutics with only favorable reports, so that such a class of preparations may fairly be considered as established for veterinary practice where the large quantities used make the reduced cost a very important consideration. Some hospitals are also still using them in increasing quantities without discoverable objection. The number of physicians known to be using them in private practice, though not yet large, is increasing, and no serious disadvantages have been developed by close and careful observation.

In selecting a drug for competitive investigation in this second paper, cinchona was selected first on account of its importance, next on account of the difficulty there has always been in finding a proper menstruum,—next on account of the difficulty of exhaustion by any menstruum hitherto known, and finally on account of the very considerable amount of time and work that the writer has

given to it for many years past in papers published from time to time in the *Proceedings of The American Pharmaceutical Association.*[1]

A fair grade of yellow cinchona was taken which, when carefully assayed by the process to be given in detail farther on, yielded 4·9 per cent. of total alkaloids, of which 2·7 per cent. belonged to the quinine group. This was carefully ground, one portion into a No. 9 powder and another portion to a No. 60 powder. Repercolation was used in exactly the same way as with nux vomica in the first paper.

For the U.S.P. No. 60 powder the U.S.P. menstruum of a mixture of eight volumes of alcohol (91 per cent.) and two volumes of glycerin (95 per cent.) was used. For the No. 9 powder a 10 per cent. acetic acid was used. A third single percolation was made of the No. 60 powder with 10 per cent. acetic acid to determine the difference in rate and degree of exhaustion between fine and coarse powder with a 10 per cent. acetic acid menstruum. The U.S.P. menstruum was adopted, first because it is the officinal menstruum, and next because it is pharmaceutically the best menstruum for extracting and holding the active principles in concentrated preparations. But therapeutically these preparations are objectionable because they are overloaded with inert extractive matter, and on dilution either before or after administration deposit copious insoluble precipitates. The percolations were managed exactly as were those with nux vomica. Each 100 c.c. fraction as it came off was weighed, and the weight of the same measure of menstruum being subtracted, the difference was noted to indicate the rate and degree of exhaustion and these differences are shown in the following table:

Each portion consisted of 500 grammes of cinchona. The first and fourth portions are single percolations with acetic acid, the only difference being in the fineness of powder, and these are compared in the fourth pair of columns. After the fifth fraction of the first portion the successive fractions were used to moisten and percolate the second portion of 500 grammes, and after the fifth fraction of the second portion the successive fractions of weak percolate were

[1] See Proceedings for 1865, p. 214.—1867, p. 391.—1870, p. 161.—1878, p. 715.—AMER. JOURN. PHARM., Vol. XXXIX, pp. 398, 408.—*Ephemeris*, Vol. I, pp. 76, 105, 146, 174.—Vol. III, p. 993.

used to moisten and percolate the third portion of 500 grammes. This third portion, being the limit to which it was decided to carry the repercolations, had all the fractions of percolate grouped together in groups of five, and these larger fractions were reserved for further comparison and for assay, each portion having been carried to practical exhaustion by fresh menstruum to follow the weak percolates.

The irregularities in progression of all the columns of the table are doubtless due to irregularities in the packing of the moistened powders and to changes of temperature.

It must not fail to be noticed that, although the rate of exhaustion is in favor of the acetic acid, it is less favorable than would appear from a casual comparison of the figures. For example, the difference in weight of 100 c.c. of the menstrua is (91·09 from 101·43) 11·06 grammes. The difference between the first pair of figures of the table is (9·39—6·28=) 3·11 grammes, or nearly one-half of the acetic acid difference, and therefore, to render these columns strictly comparable, a considerable addition is due to the figures of the acetic acid columns. But the amount of such addition is so difficult to estimate that it must be left indefinite.

The nearly uniform differences of the first fractions of acetic acid percolate from the first and second portions, and from the first three fractions of the third portion, indicate that the acetic acid menstruum is practically saturated with the constituents of the cinchona that are soluble in this menstruum, whilst the increase in the differences of the first five fractions of U.S.P. percolate of the third portion show that this menstruum has a much greater solvent capacity than the 10 per cent. acetic acid. When the difficult solubility even of the acid salts of the cinchona alkaloids is remembered this saturation is not difficult to comprehend. But when these supposed saturations were tried they were found capable of dissolving considerable quantities of the total alkaloids obtained from the assays of other portions of cinchona.

The fourth portion or final pair of columns is given for the purpose of comparing by differences the rate and degree of exhaustion in two percolations with the acetic acid menstruum, managed in exactly the same way, but differing simply in the fineness of the powder, the apparent result being that the exhaustion was more rapid though hardly more complete in the fine powder as far as the differences go.

RATE AND DEGREE OF EXHAUSTION BY DIFFERENCES.

Percolate in Successive Fractions of 100 Cubic Centimetres Each.	First Portion.		Second Portion.		Third Portion.		Fourth Portion.	
	U.S.P. No. 60 Powder. Differences Grammes.	Acetic Acid No. 9 Powder. Differences Grammes.	U.S.P. No. 60 Powder. Differences Grammes.	Acetic Acid No. 9 Powder. Differences Grammes.	U.S.P. No. 60 Powder. Differences Grammes.	Acetic Acid No. 9 Powder. Differences Grammes.	Acetic Acid No. 9 Powder. Differences Grammes.	Acetic Acid No. 60 Powder. Differences Grammes.
1st fraction .	9·39	6·28	9·41	6·40	11·58	6·43	6·28	5·49
2d " .	8·36	6·11	8·36	6·18	9·82	6·60	6·11	5·18
3d " .	6·83	5·51	7·94	5·84	8 81	6·39	5·51	5·10
4th " .	4·05	4·46	6·57	5·30	7·14	5·49	4·46	4·44
5th " .	2·64	3·33	5·51	4·40	6·03	4·62	3·33	3·60
6th " .	1·90	2·30	3·96	3·36	4·73	3·56	2·30	2·65
7th " .	1·82	1·63	3·34	2·35	4·01	2·61	1·63	2·23
8th " .	1·51	1·26	2·94	1·88	3·80	2·28	1·26	1·57
9th " .	1·40	·88	2·83	1·35	3·46	1·60	·88	1·22
10th " .	1·26	·83	2·39	1·06	3·40	1·35	·83	·97
11th " .	·73	·43	2·00	·88	3·07	1·05	·43	·70
12th " .	·44	·51	1·51	·72	2·78	1·05	·51	·74
13th " .	·64	·40	1·39	·65	2·22	·74	·40	·64
14th " .	·22	·34	1·14	·61	1·95	·89	·34	·42
15th " .	·24	·28	1·16	·56	1·50	·67	·28	·35
16th " .	·99	·69	1·02	·51	1·00	·76	·69	·45
17th " .	·67	·33	1·06	·45	·66	·69	·33	·41
18th " .	·57	·39	·80	·46	1·13	·74	·39	·34
19th " .	·46	·20	·76	·42	·94	·65	·20	·23
20th " .	·25	·28	·69	·46	·68	·54	·28	·21
21st " .	·16	·15	·94	·49	·73	·48	·15	·23
22d " .	·13	·16	·64	·35	·64	·68	·16	·17
23d " .	·13	·05	·63	·35	1·25	·51	·05	·15
24th " .	—	—	·66	·43	·85	·54	—	·06
25th " .	—	—	·43	·25	·78	·24	—	·08
26th " .	—	—	·53	·35	·58	·50	—	·06
27th " .	—	—	·46	·24	·67	·35	—	·08
28th " .	—	—	·45	·33	·40	·50	—	·04
29th " .	—	—	·39	·20	·30	·24	—	·02
30th " .	—	—	·30	·23	·14	·40	—	·09
31st " .	—	—	·23	·13	·22	·17	—	—
32d " .	—	—	·16	·08	·10	·33	—	—
33d " .	—	—	—	—	·17	·17	—	—
34th " .	—	—	—	—	·17	·19	—	—
35th " .	—	—	—	—	·10	·12	—	—
36th " .	—	—	—	—	·08	·12	—	—
37th " .	—	—	—	—	·17	·09	—	—
38th " .	—	—	—	—	·08	·04	—	—

The fractions of the above table were put together in successive groups of five fractions each, the exact measure of 500 c.c. being made up from the next percolate in succession. In this way the 100 c.c. fractions were concentrated into 500 c.c. fractions, which were weighed as well as measured and the differences taken, these larger fractions being carried through in pairs, each being assayed for the total alkaloids contained. For these assays 10 c.c. of the stronger liquids was taken and the results multiplied by 50. For the weaker liquids 20 c.c. was taken and the results multiplied by 25. Each of the three portions consisted of 500 grammes of cinchona and each large fraction consisted of 500 c.c. of percolate.

Of the first and second portions only the first 500 c.c. of percolate was reserved, the succeeding fractions from the first portion being used as menstruum for the second and those from the second portion being carried to the third portion. But all the fractions from the third portion to practical exhaustion were reserved and assayed, and if the repercolation had been carried farther these fractions would have been successively used as menstruum on a fourth portion of cinchona.

The single separate percolation, "Fourth Portion" of the table above, made for the purpose of comparing the results from the use of fine powder against coarse, does not enter the following table, as these were only comparable assays. The first 500 c.c. from coarse powder had 7·5 grammes of alkaloids, while the similar fraction from fine powder gave 8·2 grammes of alkaloid. This leads directly to the conclusion that if fine powder had been used for the principal series of comparisons the results given in the following table would have been more favorable to the acetic acid menstruum by about 9 per cent.

ASSAYS OF CINCHONA PERCOLATES.

500 gm. Portions.	500 c.c. Percolates.	U.S.P. Menstruum, 800 c.c. Alcohol, 91 p. c. 200 c.c. Glycerin, 95 "			Acetic Acid Menstruum, 10 p. c. Acetic Acid.		
		Weight Gm.	Difference Gm.	Total Alkaloids Gm.	Weight Gm.	Difference Gm.	Total Alkaloids Gm.
1st portion	1st 500 c.c.	487·9	32·0	12·1	534·0	26 8	7·5
2d "	1st " "	495·8	39·8	12·7	537·5	30·3	11·9
3d "	1st " "	499·8	44·5	19 5	537·8	30·1	14·9
" "	2d " "	475·1	19·9	9·4	519·3	11·6	9·5
" "	3d " "	468·2	13·0	4·3	511·9	4·2	6·9
" "	4th " "	460·2	5·0	2·7	510·7	3·0	5·9
" "	5th " "	459·8	4·5	2·5	510·2	2·5	3·8
" "	6th " "	457·7	2·4	1·7	509·6	1·9	3·5
" "	7th " "	456·2	1·0	1·6	509·1	1·4	3·0
" "	8th " "	—	—	1·1	—	—	1·1
" "	9th " "	—	—	0·7	—	—	0·8
				68·3			68·8
	1500 gm. Cinchona of	4·9 p. c.		= 73·5			73·5

In summarizing the results of this work the following conclusions are reached and adopted:

That 10 per cent. acetic acid is a good menstruum for the exhaustion of cinchona.

That the U.S.P. menstruum is a better one for rapid exhaustion, but the percolates are so loaded with useless and objectionable organic matters, from which the acetic acid percolates are comparatively free, that this difference in the character of the results transfers the advantages to the acetic acid side. The stronger percolates from the alcohol and glycerin menstruum are almost syrupy in consistence, are so black as to be almost intransparent, are very astringent, and throw down an unmanageable precipitate of nearly insoluble cincho-tannates on dilution or admixture with other preparations or any ordinary diluents. These disadvantages are of so serious a character as to have always obstructed the use of the officinal fluid extract and extract.

The acetic acid stronger percolates are nearly free from these disadvantages, and are far more manageable pharmaceutically as well as therapeutically. It is hardly within the range of possibility that

a fluid extract or extract which on dilution splits up into insoluble or difficultly soluble cincho-tannates can be a good therapeutic agent, or that a preparation of the same alkaloidal strength that does not so split on dilution is not better.

The difference in the cost of the two menstrua is very great, the alcoholic menstruum costing about eight times as much as the acid, whilst the acid is much easier to manage in the percolation and in the standardizing process, since evaporation does not injure the percolates nor materially increase the cost by the loss.

The U.S.P. standardizes its preparations of yellow cinchona in an indirect way by requiring that the cinchona from which they are made shall contain not less than 5 per cent. of total alkaloids and at least 2·5 per cent. of quinine, by an assay process which it gives, wherein a chloroform extract is weighed as total alkaloids. Although this is not the only objection to this assay process, it secures a cinchona powder that should contain at least 5 per cent. of total alkaloids, equal to 50 grammes in 1,000, or 25 grammes in 500. The cinchona used for this investigation contained 4·9 per cent. of total alkaloids equal to 49 grammes in 1,000, or 24·5 grammes in 500, or say in 500 c.c. for facility of comparison, although this 500 c.c. weighs 534 grammes.

The U.S.P. requires for its fluid extract that 1,000 c.c. should represent 1,000 grammes of 5 per cent. cinchona, or 500 c.c. containing 25 grammes of alkaloids from 500 grammes of cinchona. No one of the first percolates from either portion by either menstruum comes up to this officinal requirement, but those by the acid menstruum were easily brought to it by evaporation.

The first 500 c.c. of the first portion was evaporated to 150 c.c., and then contained the proportion of 25 grammes of alkaloids in 500 c.c.

The first 500 c.c. of the second portion was evaporated to 238 c.c., and then contained the officinal proportion of 25 grammes of alkaloids in 500 c.c.

The first 500 c.c. of the third portion was evaporated to 298 c.c., and then contained the officinal proportion of 25 grammes of alkaloids in 500 c.c.

In the first of these three the loss in standardizing by evaporation was greatest, and then it amounted to about 350 grammes of 10 per cent. acid, at a cost of less than 4 cents. But this is a maximum loss that in practice could rarely exceed half this amount.

In assaying these largely evaporated extracts before the evaporation and after, very slight loss of alkaloids was discovered, and it is believed that these are fairly safe in acid solution with no greater heat than a water-bath.

This point is in favor of the acid menstruum, since it is the common experience that evaporation with alcoholic menstrua generally reduces the proportion of alkaloids, changing them and probably oxidizing them as is not probable with acid salts and solutions of most alkaloids.

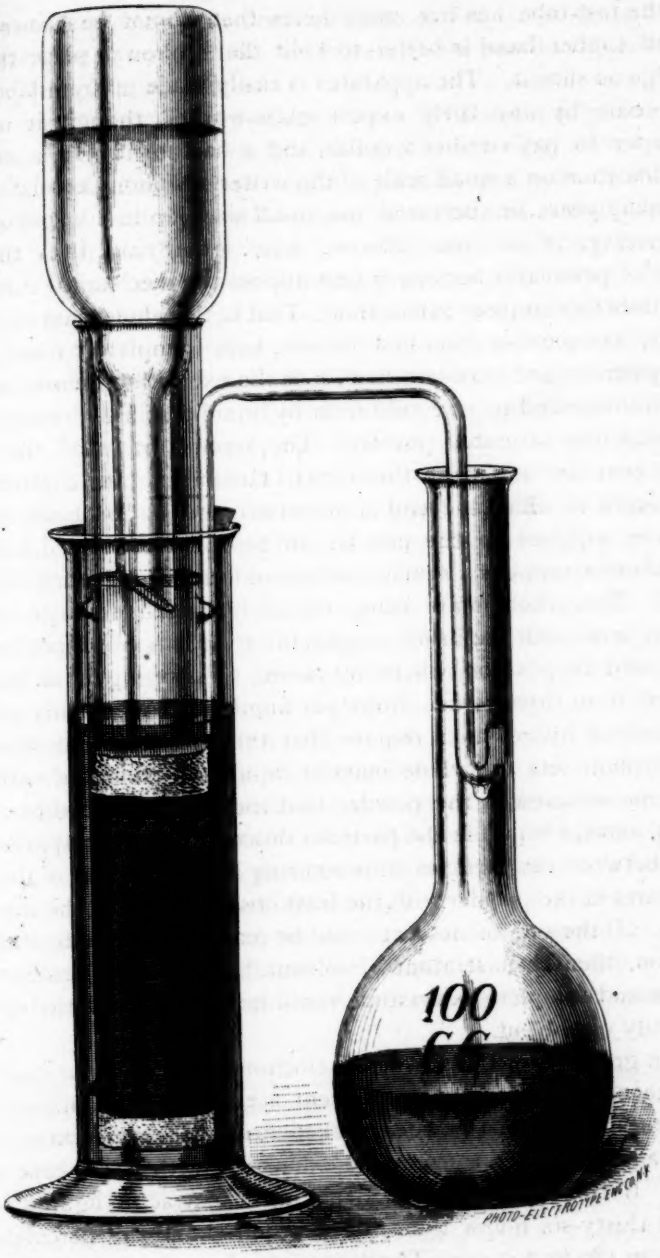
It was desirable to know with a fair degree of accuracy how much free acid an acetic acid fluid extract of cinchona with this menstruum would contain, and in the above-described three portions of fluid extract the proportion was found to be 11, 10·2 and 10 per cent., and where there had been most evaporation there was least free acid. The lowest of these proportions is quite sufficient to secure the stability and permanency of the preparations under all ordinary conditions. When this fluid extract is mixed with three or four times its volume of water, the mixture has the appearance of coffee with milk, and in this condition the taste of free acid is very slight and not disagreeable, and the conclusion is reached that in all discovered ways it is a better therapeutic agent and a more eligible preparation than the officinal fluid extract and at far lower cost.

THE ASSAY PROCESS FOR CINCHONA.

The cinchona should be in fine powder for complete exhaustion, and the harder the bark the finer the powder should be. The U.S.P. directs a No. 60 powder for its preparations, but No. 80 or finer for its assay process. The B.P. directs No. 60 for both preparations and assay. But the results obtained here by the use of 10 per cent. acetic acid as a menstruum show that complete exhaustion is easily obtained with a No. 9 powder for the assay process.

The apparatus and management are, however, of great importance in obtaining complete exhaustion if the residue is to be, as it should be, bitter-free when well chewed. This is so difficult and of so much importance that it appears to be worth while to offer a cut of an extractor that has been very successful in the extraction of nux vomica and now in the still more difficult cinchona, and that is expected to be equally applicable to many other substances.

This simple apparatus is shown in operation. The flattened end



EXTRACTOR.

of the test-tube has five small holes that cannot be shown, and a small rubber band is better to hold the syphon in place than the wedge as shown. The apparatus is easily made up from laboratory materials by any fairly expert glass-worker, though it may be cheaper to pay Greiner a dollar and a half for it. It is simply a modification on a small scale of the writer's syphon percolator, now so many years in successful use, in all sizes up to 100 gallons (see *Proceedings of the Amer. Pharm. Assoc.* for 1872). It is the best form of percolator because it best applies the mechanical conditions requisite for complete exhaustion. That is, the whole mass of powder to be extracted is, from first to last, kept completely filled, inside the particles and between them, with the extracting menstruum and counterbalanced to an equilibrium by liquid that has already passed through the saturated powder. The syphon draws off the liquid from near the surface of this outer column at a rate controlled by the depth to which the end is immersed, and by the head of menstruum supplied to the powder on top. The inverted bottle of menstruum supplies a nearly continuous feed from a nearly constant level. The whole mass being full of liquid, the outside column nearly level with the inside supply, the syphon is filled, put in place and held in position, where by raising or lowering it is made to deliver from three to five drops per minute. Now, in this position the laws of hydrostatics require that the first drop that falls from the syphon sets the whole mass of liquid in motion, but with such extreme slowness in the powder that friction is reduced to a minimum, and the liquid in the particles descends at a rate approaching that between the particles, thus securing a displacement of the soluble parts of the powder with the least obstruction from the insoluble parts. If the rate of descent could be made so slow as to eliminate friction, then each stratum of solvent liquid would descend as a piston and complete exhaustion would be attained with the smallest quantity of solvent.

Ten grammes of the powdered cinchona in a capacious capsule is moistened with 10 c.c. of 10 per cent. acetic acid, the lumps all well broken up, the moist powder packed firmly in some form of percolator and percolated to complete exhaustion with 10 per cent. acetic acid. If this exhaustion be done in the extractor figured above, about thirty-six hours' time will be required and the percolate will measure 180 to 200 c.c. The degree of exhaustion is judged by the

degree of bitterness of the final percolate, which is not quite bitter-free when the cotton and the lower part of the powder is quite bitter-free though not tasteless.[1]

The entire percolate is evaporated in a flat-bottom capsule to the condition of a soft solid when cold, capable of being stirred when hot. This extract usually weighs 35 to 38 per cent. of the cinchona and it retains a small amount of acetic acid. While heated on the water-bath, 30 c.c. of a previously made mixture of 5 volumes of 10 per cent. water of ammonia and 15 volumes of 91 per cent. alcohol is added, the mixture is stirred to a uniform condition and poured into a separator of 160 to 180 c.c. capacity. The capsule is rinsed into the separator with a mixture of 10 c.c. of the ammonia mixture and 10 c.c. of alcohol, and the whole is well shaken together. If much ammonia has been lost in dissolving the extract —if much acetic acid should have been retained in the extract, or if the cinchona should be very rich in alkaloids, the 40 c.c. of ammonia mixture may be insufficient to set the alkaloids free. This point is always to be assured by the smell of ammonia at the mouth of the separator, or by holding a strip of wet and neutral litmus paper in the air space of the separator. If the alkaline reaction be not full and prompt, 5 c.c. more of the ammonia mixture is added and the shaking and testing repeated.

Then 40 c.c. of chloroform (96 per cent.) is poured into the separator, the whole is vigorously shaken for five minutes and then allowed to separate. This separation requires ten to fifteen minutes and then the chloroform solution is drawn off into a tared flask of about 100 c.c. capacity, and is put upon the water-bath to boil off the chloroform. Then 5 c.c. of alcohol (91 per cent.) is added to the residue in the separator, is shaken in, and then a second 40 c.c. of chloroform is added, and the whole is again shaken for five minutes, allowed to separate, the chloroform drawn off into the tared flask

[1] In these percolations, especially when on a larger scale, it is difficult to get a bitter-free final percolate and residue, so that it was desirable to know how much bitterness was consistent with practical exhaustion. A solution of total alkaloids of cinchona of one part in 100,000 of water was made, and this was perceptibly though faintly and transiently bitter to several, but not to all ordinary tastes. This, therefore, is not bitter-free. One part in 10,000 was distinctly and rather permanently bitter, and as this is but 0·01 of 1 per cent., it is considered, on the large scale, as practical exhaustion.

with the first portion, and the whole of the chloroform boiled off in the bath. If the alcohol be omitted from the residue before this second washing, an emulsion is almost certain. The apparent excess of chloroform is necessary not so much for the washing out of the alkaloids as to avoid emulsion. The residue is run off from the separator into a beaker, is well stirred, five or six drops is transferred by the stirrer to the end of a strip of bibulous paper and dried on the bath. This, when taken into the mouth and well chewed, should be bitter-free.

The chloroform solution, when the chloroform, ammonia and alcohol are boiled off, leaves a very dark residue in the flask usually weighing about 1 gramme. This is dissolved in 20 c.c. of chloroform by shaking, and 10 c.c. of water added and shaken. Then 20 c.c. of decinormal sulphuric acid is run into the flask from a burette, shaken for five minutes and poured into a separator. When the liquids separate the lower, chloroform part, is drawn off into the flask again and the upper watery portion into a beaker. Then 10 c.c. more of decinormal acid and 5 c.c. of water are added to the contents of the flask, the whole well shaken for five minutes, returned to the separator, the flask rinsed in with 5 c.c. of water, and the whole well shaken in the separator. When the liquids separate, the lower chloroform residue is drawn off into a small beaker, and the watery portion into the beaker with the first watery portion. The chloroform residue is now tested by drying upon bibulous paper, as before described, and if found bitter-free it is thrown away, but if still bitter to the taste it is again washed.

To the acid-watery solution in the larger beaker 30 c.c. of decinormal potassium hydrate is added with stirring, the whole transferred to the separator, 25 c.c. of ether (96 per cent.) added and the mixture well shaken. When the liquids separate, 5 c.c. of decinormal alkali is poured into the separator, producing a large precipitate that is redissolved when shaken. This addition of decinormal alkali is repeated until one addition fails to produce cloudiness. Then the mixture is shaken for five minutes, allowed to separate and the lower watery liquid is drawn off into the larger beaker. The ether solution cannot be drawn off clean through the stopcock, but can be poured off through the mouth of the separator, to the last drop, into a tared beaker, leaving a little emulsion and water drops behind. To these residues in the separator 20 c.c. of ether is added

and well shaken, the watery solution from the large beaker added, again shaken for five minutes, allowed to separate, drawn off and poured off as before, and this washing is repeated a third time.

The watery portion is now tested and should be found bitter-free, or be again ether-washed. The ether solutions in the tared beaker are boiled off on the bath and leave a varnish-like residue of an amber color, consisting of total alkaloids and a little insoluble waxy matter. This is weighed in order to get the approximate percentage of alkaloids, and for each 1 per cent. of these crude alkaloids 5 c.c. of decinormal acid is run into the beaker from a burette and 10 c.c. of water added. But these alkaloids are difficult and slow to dissolve in the acid, so that time is saved by dissolving them in 3 or 4 c.c. of ether by rotary agitation before the acid is run in. When the acid is run in, the waxy and fatty matters are precipitated and a stirrer and warming are then used to free this precipitated matter from alkaloids and to drive off the ether. The alkaloids are thus converted into acid salts and dissolved, and the insoluble matters are deposited on the sides and bottom of the beaker. If the nearly clear solution be poured off and the beaker and residue be dried, weighed and the weight be subtracted from the weight of crude alkaloids, the remainder will be within 0·1 or 0·2 per cent. of the weight of pure alkaloids, and thus will be a useful check upon the titration that is to follow.

In the titration now to be described litmus paper is used as the indicator, and if the paper be good and be well managed the indication is sufficiently accurate, reaching to the second decimal place of percentage. The paper is used in strips 0·5 cm. wide, some of deep blue, some neutral, and about a centimetre of the end of the strip is wetted for the indication.

Decinormal potassium hydrate solution is dropped from a burette into the acid solution of the alkaloids with stirring and frequent testing until the solution fails longer to change blue litmus paper. When the blue strip is just touched to the surface of the solution, the liquid rises in the paper to about a centimetre. As the neutral point is approached the end will be blue with a red or reddish band above the blue, but when it is reached the whole wetted part will be unchanged blue. Then a strip of neutral litmus paper has the end wetted with distilled water for about a centimetre, and this end is just touched to the surface of the solution and held there for a

few seconds. On close inspection by reflected light no difference in tint between the lower and upper parts of the wetted portion will be discoverable. If this be the case, one or two drops more of the decinormal alkali is added and the testing repeated with a new strip of wetted neutral paper. Now, a small patch of faint bluish tint will be discoverable about the middle of the wetted portion, and this indicates as nearly as need be the point when all the acid salts have been reduced to neutral salts.

The number of cubic centimetres of decinormal alkali used to reach this point subtracted from the number of cubic centimetres of decinormal acid taken for the solution gives the number of cubic centimetres of the acid saturated by the alkaloids to form the neutral salts, and this number divided by 10 gives the amount of normal acid equivalent to the decinormal acid used. This multiplied by the normal molecular weight of the alkaloids would give the weight of alkaloids obtained from the 10 grammes of cinchona taken. But there are many alkaloids of different molecular weights in cinchona, so that it is impracticable to get a molecular weight that would accurately represent any sample of total alkaloids. Perhaps the best that can be done, as has often been done before, is to make an arbitrary composite combining number. All that can be said of this proceeding is that it is very convenient—that it admits of titration—that the results cannot be more than about 0·3 per cent. from the truth in rare cases, and that it is always closer than is the weighing of a chloroform or ether extract as total alkaloids.

The alkaloids of cinchona may be usefully divided into three groups:

(1) The quinine group with a molecular weight of about 0·324.

(2) The cinchonine group with a molecular weight of about 0·294.

(3) The remaining alkaloids with a molecular weight of about 0·312.

Practically no cinchona for pharmaceutical uses should contain less than 5 per cent. of total alkaloids, and at least 2·5 per cent. of these should be of the quinine group, 1·25 per cent. of the cinchonine group, and 1·25 per cent. of the remaining alkaloids. This proportion being arbitrarily assumed gives a combining weight of 0·314 as follows:

Quinine group	0·324 ÷ 2 = 0·162
Cinchonine group	0·294 ÷ 4 = 0·074
Other alkaloids	0·312 ÷ 4 = 0·078
Adopted average molecular weight	0·314*

This 0·314, then, is adopted as the factor for total alkaloids in this investigation, and an example will illustrate its use in this paper.

A recent critical assay of 10 grammes of cinchona by this process gave a varnish-like ether extract that weighed 0·53 gramme, equal to 5·3 per cent. of crude alkaloids. This indicated (5 × 5 =) 25 c.c. of decinormal acid required for dissolving the alkaloids. But these were first dissolved in 4 c.c. of ether, then the acid run in from a burette, well stirred and warmed to drive off the ether and cause the insoluble matters to adhere to the glass.

Into this solution decinormal alkali was dropped from a burette with stirring until the neutral point was reached, as indicated by the use of the litmus paper strips, when it was found that 9·3 c.c. of decinormal alkali had been used. Then 25 c.c. of decinormal acid less 9·3 c.c. of decinormal alkali leaves 15·7 c.c. of the acid as saturated by the alkaloids. Then the result is expressed as follows:

$$15{\cdot}7 \div 10 = 1{\cdot}57 \times {\cdot}314 = {\cdot}49298 \times 10 = 4{\cdot}9 \text{ per cent. alkaloids.}$$

The nearly clear solution was poured off from the residue in the beaker, and the residue when dried weighed 0·03 gramme. Then 0·53 gramme of ether extract or crude alkaloids less 0·03 gramme of waxy residue left 0·50 gramme of alkaloids, or 5·0 per cent. against 4·9 per cent. by the titration.

In the numerous assays of percolates for the purposes of this paper, a short cut was found which, without much sacrifice of accuracy, greatly reduced the time and labor required, and seems well adapted to pharmaceutical use.

Ten c.c. of the liquid preparation of cinchona is shaken in a separator, first with 20 c.c. of the ammonia-alcohol mixture, and then with 30 to 40 c.c. of chloroform, the liquids separated as in the preceding assay process, which is then followed up to the point of dissolving the chloroform extract in a fresh portion of chloroform in the flask. If the chloroform extract be under 1 gramme, 10 c.c. of fresh chloroform is sufficient for its solution in the flask, and to this is added 10 c.c. of decinormal acid. The flask is vigorously shaken, 10 c.c. of water added, the shaking repeated and the contents

poured into a separator. When separated the chloroform is drawn off into the flask again and the acid solution into a beaker. To the chloroform in the flask 2 c.c. of decinormal acid is added from the burette, well shaken, 5 c.c. water added, the shaking repeated, the whole returned to the separator, the flask rinsed in, and when separated the chloroform is drawn into a small beaker and the watery solution into the beaker with the first portion. The chloroform should then be bitter-free or be again washed. The watery solution in the beaker is now titrated with decinormal alkali.

This process answers fairly well even with the disturbing element of glycerin in the liquid, as when the U.S.P. menstruum is used, for the emulsion always formed can be titrated, and is broken up as the decinormal alkali is dropped in with vigorous stirring.

Some of the advantages claimed for this assay process are: (1) The complete and easy exhaustion of the cinchona, even when in coarse powder, by 10 per cent. acetic acid. (2) The success of the shaking out without emulsion by the use of large quantities of chloroform and very little water, and (3) by the control of loss by having all the residues bitter-free before they are thrown away.

THE ASSAY OF BELLADONNA LEAVES.[1]

By Frank X. Moerk.

In the March issue of the American Journal of Pharmacy, the writer, in an article on "The Assay of Belladonna Leaves and Some of its Preparations," called attention to the fallacy of Keller's assay process, and to the difficulty of extracting the leaves with 95 per cent. alcohol, and proposed a process in which complete extraction of the leaves with the official fluid extract menstruum (2 vols. alcohol and 1 vol. water) and completion of the assay with the entire quantity of extract was recommended. The objections to this process were stated to be the time required for its execution, and some difficulties due to the presence of so much extractive matter, namely, the emulsification of the alkaline extractions (corrected by the use of stearic acid), the separation of a pulverulent precipitate (removed by filtration) and the presence of chlorophyl in the alka-

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[1]Read at the Meeting of the Pennsylvania Pharmaceutical Association, June, 1899.

loidal residue, which occasionally interfered with the titration; the advantage of the process, the accuracy of the assay, were considered sufficient to make the first objection, practically the only one which at that time could not be corrected, appear insignificant.

Since the publication of the above paper, experiments have been in progress which tend to improve this assay process in several directions. In the first place, it was found that a menstruum made up of 90 parts by weight of 95 per cent. alcohol, and 10 parts by weight of 10 per cent. water of ammonia constituted a superior solvent; 200 c.c., by immediate percolation, extracting 20 grammes drug better than 300 c.c. of the menstruum previously used with frequent periods of maceration. The extract obtained from this percolate can be perfectly removed from the capsule and transferred to the separator by using 0·5 c.c. water of ammonia and 10 c.c. water in portions of 1 and 2 c.c. The presence of chlorophyl in the alkaloidal residue can be prevented by filtering the acid extractions, as was proved by the fact that in the twenty-two assays made in connection with this paper not a single instance was noted in which there was any difficulty in the final titration. The pulverulent precipitate mentioned in the previous article was not met with in these assays. What at first appeared to be an objection to the use of this solvent was the tendency to form persistent emulsions in the alkaline extractions which did not break upon the addition of stearic acid and agitation; this was remedied by stirring the emulsified layer with a piece of iron wire, upon the end of which a little stearic acid had been fused and allowed to cool; by drawing off the clear portion and repeating the operation several times, if necessary, almost the entire quantity of solvent can be separated; it may happen that the last portions of the emulsion will be so thick that further separation will not take place; in this case, by gentle agitation, mix the emulsion with the aqueous solution and, after allowing to separate, it will be found that the stearic acid will again perform its function. These various improvements give an assay process as follows:

Moisture.—Determined in 2 grammes at 100° C.

Assay proper.—A small, slightly conical percolator, about 8 inches long and 1¼ to 1½ inches diameter, is connected with a small piece of rubber tubing having a small piece of glass tubing attached; into this percolator introduce a plug of absorbent cotton of such size as

to practically fill up the neck of the percolator; compress the rubber tubing with a pinch-cock, to allow preparation for the percolation. Place 20 grammes of the powdered leaves in the percolator, add 50 c.c. menstruum [alcohol (95 per cent.), 180 grammes; water of ammonia (10 per cent.), 20 grammes] and stir with a heavy iron wire until a homogeneous mixture results, and in such a manner that the air-bubbles are brought as completely as possible to the surface; rinse the wire and sides of the percolator with 10 c.c. of the menstruum and allow percolation to proceed at once; add more menstruum from time to time in quantities of 20 to 30 c.c. until 200 c.c. have been used, allowing the portions to flow down the sides of the percolator to avoid stirring up of the drug. Collect the first portions of the percolate, about 100 c.c., in a porcelain dish of about 150 c.c. capacity, and the last portions in a beaker; place the dish with contents upon a water-bath, the temperature of which is kept at from 50° to 60° C., and as the solvent evaporates add the weaker percolate; continue heating until the odor of alcohol is no longer recognizable after stirring. Make a mixture of 0·5 c.c. water of ammonia and 10 c.c. water and use this in portions of 1 to 2 c.c. to soften the extract and transfer it to a separator (250 c.c. capacity), add 50 c.c. of an ether-chloroform mixture (ether 4 parts, chloroform 1 part by weight) and agitate; now add 25 c.c. acidulated water (2 c.c. H_2SO_4, U.S.P., diluted with water to 500 c.c.), using this to rinse the dish from which the extract has been removed, agitate thoroughly, and after separation of the liquids allow the acid solution to run through a small filter (5·5 cm. in diameter) into a beaker; repeat with 15, 10 and 5 c.c. acidulated water. Collect the first three portions together, reserving the last portion to rinse the beaker containing the first portions; clean the separator, introduce the acid solutions, finally rinsing the beaker with 5 c.c. water, add 25 c.c. chloroform-ether (chloroform 2 parts, ether 1 part by weight) and 8 c.c. water of ammonia and agitate thoroughly (should an emulsion form, proceed as described in the earlier part of this paper); after separation transfer the chloroform-ether solution to a smaller separator (about 100 c.c. capacity) and repeat the extraction with 15, 10 and 5 c.c. of the solvent; while this last portion is separating, run the other portions through a small filter into a clean, dry flask of about 120 c.c. capacity; rinse the smaller separator with the last extraction and transfer to the

filter; the stem of the larger separator is rinsed with 5 c.c. of the solvent and this portion used to again rinse the smaller separator before transferring to the filter; now rinse the stem of the smaller separator with a few cubic centimetres of the solvent, allowing this portion to run into the filter, and wash the filter and funnel with several small portions of solvent. Any aqueous solution transferred to the smaller separator should be prevented from getting on the filter and the latter should be covered as much as possible to prevent evaporation of the solvent.

Distil off the solvent on a water-bath, warm until the odor of chloroform disappears, dissolve the residue in 5 c.c. ether, evaporate, redissolve residue in 5 c.c. ether, evaporate and heat until the odor of ether disappears; dissolve in 8 c.c. neutral alcohol, add 30 c.c. water and 3 drops hæmatoxylin solution and titrate with standardized HCl to the disappearance of any red shade or the formation of a pure yellow color.

The results of this process [(1) and (2)], compared with those obtained by the original process [(3) and (4)], show slightly higher results, particularly if differences in percentages of moisture are considered.

	Moisture (1) Per Cent.	Alkaloid (2) Per Cent.	Moisture (3) Per Cent.	Alkaloid (4) Per Cent.
Powdered leaves, B.	9·15	{0·4944 0·4997	9·15	{0·4839 0·4891
English cultivated	8·85	0·6312	8·40	{0·5996 0·6040
German cultivated	8·43	0·5155	7·60	{0·5155 0·5050
German wild, I	8·50	—	6·80	{0·4997 0·4997
German wild, II	8·60	0·4208	—	—
Powdered leaves, K.	7·60	0·3629	—	—

The knowledge that the solvent used in this process is homogeneous and perfectly miscible with water suggested the possibility of using an aliquot portion of a maceration to complete the assay, thus saving additional time. One of the most important objections to assay processes in which an aliquot portion is used to represent a definite weight of drug is the increase in weight of the solvent added, by the moisture and soluble matters taken up from the drug, and for which no allowance is made in some processes, or a uniform allowance is made for all samples of a drug regardless of the actual

quantities of moisture or extractive. In the following work an allowance of 2 grammes extractive was first made for 20 grammes drug, hence 98 grammes solvent were used; by making a moisture determination and also weighing the extract obtained from the aliquot portion of the solution, it is possible to make a correction for the presence of a different quantity of extractive; the extract obtained under the conditions of the assay process will contain approximately 15 per cent. moisture and 85 per cent. solid matter. By adding the percentages of moisture in the leaves and of dry extract and calculating to 20 grammes, there is obtained the total extractive taken up from the drug and this, added to the weight of the solvent used in the assay, will give the total amount of solution from which an aliquot part was used to complete the assay. From the tabular statement of results it will be noticed that the extractive in the samples examined varied from 3·5 to 4·5 grammes, instead of the 2 grammes first allowed, and the alkaloid found corrected for this gives figures closely agreeing with the results of the more lengthy total extraction processes.

Based upon the work as embodied in the table, the following shorter process is suggested, allowing 3·5 grammes for extractive:

Moisture.—Determined in 2 grammes leaves at 100° C.

Alkaloidal Assay.—20 grammes of powdered belladonna leaves are placed in a glass-stoppered bottle of 250 c.c. capacity and 96·5 grammes solvent [alcohol (95 per cent.), 90 parts; water of ammonia (10 per cent.), 10 parts] added; agitate frequently during one-half to one hour and filter through a plaited filter (15 cm. diameter) into a clean, dry flask, keeping the filter covered as much as possible to avoid evaporation. Weigh the flask with contents and transfer solution to a capsule of about 150 c.c. capacity, in which a small glass rod has been placed, and which have previously been weighed; weigh the emptied flask and note the difference in the two weights as that of the aliquot portion for the assay. Evaporate on a water-bath at a temperature of 50° C. until the extract, after cooling, can no longer be stirred with the glass rod; weigh the capsule and contents, thus ascertaining the weight of the extract from which the percentages of extract and dry extractive can be calculated [(6) and (7) of table]. Mix 0·5 c.c. water of ammonia and 10 c.c. water and use this in portions of 1 and 2 c.c. to soften the extract and transfer to the separator, and proceed according to directions previously given in this paper (page 322).

		(1) Extractive allowed.	(2) Solvent added.	(3) Aliquot portion for assay.	(4) Drug represented by (3) (without correction) (3) ÷ 5.	(5) Alkaloid found × 100 ÷ (4).	(6) Extract from (3) × 100 ÷ (4).	(7) Dry extractive in (6) (6) × 0·85.	(8) Moisture in leaves.	(9) Calculated total extractive from 20 gms. drug (7) + (8) × 0·20	(10) Total solution in assay (2) + (9).	(11) Factor for correcting (5).	(12) Corrected alkaloidal percentage (5) × (11).	(13) Alkaloid by total extraction.
		Gms.	Gms.	Gms.	Gms.	Per cent.	Per cent.	Per cent.	Per cent.	Gms.	Gms.		Per cent.	Per cent.
German Cultivated.	*a.*	2	98	58·520	11·704	0·5033	14·95	12·71	8·43	4·228	102·228	1·0223	0·5145	0·5155
	b.	2	98	60·700	12·140	0·5026	15·07	12·81		4·246	102·246	1·0225	0·5139	
	a.	2	98	57·180	11·436	0·4967	14·43	12·26		4·138	102·138	1·0214	0·5073	
	b.	2	98	59·400	11·880	0·5047	14·39	12·23		4·132	102·132	1·0313	0·5154	
English Cultivated.	*a.*	2	98	54·450	10·890	0·6086	16·07	13·66	8·85	4·502	102·502	1·0250	0·6238	0·6312
	b.	2	98	55·580	11·116	0·6151	16 01	13·61		4·492	102·492	1·0249	0·6304	
German Wild, I.	*a.*	2	98	61·740	12·348	0·4856	11·01	9·36	8·50	3·572	101·572	1·0157	0·4932	0·4997
	b.	2	98	61·280	12·256	0·4893	11·50	9·77		3·655	101·655	1·0165	0·4973	
German Wild, II.	*a.*	0	100	53·380	10·676	0·3941	10·49	8·91	8·10	3·502	103·502	1·0350	0·4079	0·4208
	b.	2	98	55·770	11·154	0·4055	11·03	9·37		3·594	101·594	1·0159	0·4120	
Powdered Leaves, B.	*a.*	2	98	64·180	12·836	0·4835	10·62	9·03	9·15	3·636	101·636	1·0163	0·4914	0 4944
	b.	2	98	66·200	13·240	0·4847	10·87	9·24		3·678	101·678	1·0168	0·4929	0·4997
Powdered Leaves, K.	*a.*	3·5	96.5	69·260	13·852	0·3570	12·06	10·25	7·60	3·570	100·070	1·0007	0·3572	0·3629
	b.	3·5	96·5	69·240	13·848	0·3570	12·27	10·43		3·606	100·106	1·0011	0 3573	

The assays in which one-half hour and one hour maceration was allowed are marked in the table *a* and *b* respectively; the statement made that the mixture of alcohol and ammonia is a superior solvent is confirmed by the slight differences noted in these duplicate assays.

BISMUTH SUBGALLATE; ITS HISTORY, CHEMICAL COMPOSITION AND PROPERTIES.

By Lyman F. Kebler.

Research Committee E, Pharmacopœia Revision.

There are probably few chemicals around which there clusters so much that is interesting as bismuth subgallate. The interest manifests itself in the history of its preparation, its chemical composition and chemical properties, the rôle it has played in our patent laws, and its value as a therapeutic agent.

In 1841, H. Bley[1] prepared, described, analyzed and assigned a chemical formula to this compound. In order that there may not be any misunderstanding, those portions of the original communications or patents which are of especial interest will be reproduced in this paper. "Um *gallussaures Wismuthoxid* darzustellen, wurde eine Lösung von basisch—essigsaurem Wismuthoxid in vieler überschüssiger Essigsaüre nebst Salpetersaure mit einer warmer Lösung von Gallussäure im Ueberschuss versetzt, wodurch sich ein hellgelber Niederschlag erzeugte." On analysis he found the precipitate to contain 51·48 per cent. of bismuth oxide and assigned to it the following formula: $2BiO + G + 2$ aq.

The directions of Bley for preparing bismuth subgallate are not given in detail, yet the following method, based on his outlines, gave the writer a very good article. To 300 grammes of bismuth subnitrate, in a container, add 100 grammes of nitric acid (sp. gr. 1·38) and 350 grammes of 80 per cent. acetic acid, agitate and, when solution is effected, dilute with 8 litres of distilled water; mix well and add, while stirring, 200 grammes of gallic acid, previously dissolved in 8 litres of luke-warm, distilled water. Wash the resulting precipitate with distilled water by means of decantation, until the wash-water only slightly affects blue litmus paper. On draining and

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[1] 1841, *Arch. der Pharm.*, *26*, 169; Abstr. L. Gmelin's Hand-book of Chemistry, 1859, Vol. *12*, p. 409.

properly drying the precipitate, a soft canary-yellow product was the result. It compared favorably with any commercial article, and an analysis showed it to contain 53·81 per cent. of bismuth oxide.

Fifty years later, B. Fischer[1] prepared the same article as follows: Dissolve 15 parts of bismuth nitrate crystals in 30 parts of glacial acetic acid, dilute with from 200 to 250 parts of water, and filter. To this filtrate add, with constant stirring, a warm solution of 5 parts of gallic acid dissolved in from 200 to 250 parts of water. The resulting precipitate is allowed to subside, the supernatant liquid decanted, the precipitate transferred to a strainer and washed with water until the wash-water no longer gives a reaction for nitrates with diphenylamine.

It is quite difficult to so thoroughly remove the nitrates from the bismuth subgallate by washing that the extremely searching reagent diphenylamine will no longer indicate their presence.

In 1897 two patents were taken out on bismuth subgallate, one in France and the other in the United States. The French patent covers a process for its manufacture, and intends the article to be used as a pigment. The American patent covers not only the process of manufacture, but the chemical product itself, even to the per cent. of bismuth it contains, and intends it as a therapeutic agent.

The French patent,[2] granted to "A la Compagnie parisienne de couleurs d'aniline," reads as follows: "48 kilogrammes de nitrate de bismuth neutre sout dissous dans de l'acide nitrique délayé, et cette dissolution est additionneé d'une dissolution de 19 kilogrammes d'acide gallique dans 40 litres d'alcool et 20 litres d'eau. Puis on ajoute de l'alcali caustique, de l'alcali carbonique on des corps similaires jusqu'à ce que le reaction ne soit plus que facilement acide; aussi l'addition d'acetate de soude, même l'addition d'eau, provoque la précipitation.

"Le précipité obtainu est du gallate du bismuth basique et a la formule

$$Bi\begin{cases}(OH)_2\\ CO_2C_6H_2(OH)_3\end{cases}$$

"La théorie demande 50·4 p. 100 de (Bi), nous avous trouvé 49·4 p. 100 de (Bi). Il se présente sous forme d'une poudre jaune, insoluble dans l'eau et dans des acides délayés.

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[1] 1891, *Pharm. Ztg.*, p. 400; Abstr. in AMER. JOUR. PHARM., *63*, 408.

[2] 1891, Apr. 11, Brevet No. 212,712, Vol. 78, Part II, p. 44.

"Dans le procédé déscrit, l'acide gallique peut être remplacé par n'importe lequel de ses sels neutres solubles dans eau."

About two and one-half months after the appearance of the above patent, application was made in this country for a patent on the same article. This, however, was only granted after a number of demurs. From the reading of the two patents it would seem that the American is a translated copy of the French brevet.

The United States patent,[1] granted to A. Liebrecht, two years after filing, reads as follows:

"Basic gallate of bismuth, a compound not known before. Forty-eight parts by weight of neutral nitrate of bismuth are dissolved in diluted nitric acid and thereto is added a solution of nineteen parts by weight of gallic acid in forty parts by weight of alcohol and twenty parts by weight of water. To the mixture is added caustic alkali, alkali carbonate, or the like, until the whole remains but slightly acid. On the addition of acetate of soda, and even on diluting with water, precipitation takes place. The precipitate thus obtained is basic gallate of bismuth having the formula:

$$Bi\begin{cases}(OH)_2\\ CO_2C_6H_2(OH)_3\end{cases}$$

Of bismuth, which according to theory should amount to 50·4 per cent., 49·4 per cent. are found in the product, which is in the form of a yellow powder insoluble in water and dilute acids. For the gallic acid in the above example may be substituted any of its neutral salts, which are soluble in water."

According to the patent, the exclusive right is given the patentee to the chemical name, even to the very percentage composition. In no other progressive country is such a thing possible.

From a reading of the above patents one is forced to the conclusion that the United States document is translated and copied almost verbatim, literatim, et punctatim. According to our patent laws a patent can be secured on anything new and useful, provided the same has not been patented or used for a period of more than two years prior to the date of application in this country. The copying of the French patent and securing a grant therefor in this country is, therefore, not illegal, but is, nevertheless, a questionable act.

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[1] U. S. Patent No. 495,497, Apr. 18, 1893, filed June 25, 1891.

The history of the preparation of bismuth subgallate indicates that the United States patent would not stand long should opposition come. In due time the patent was attacked, and one manufacturer after another began to put the article on the market, yet, as far as the writer knows, the patent has neither been officially annulled, nor have the patentees maintained a rigorous legal defence. In consequence almost every manufacturer is supplying the article.

From this condition of affairs it might seem that articles of great variation would be met with in the channels of trade. This, however, is not the case with this article, as the following table will show:

No.	Physical Appearance.	Microscopical Appearance.	Per Cent. of Bismuth Oxide, Dried at 63° C.	Per Cent. of Volatile Matter at 110° C.	Reaction on Litmus Paper.	Solubility in 10 Per Cent. KOH.
1. . .	Soft, bright yellow powder.	Amorphous.	53·40	2·8	Acid.	Soluble.
2. . .	Soft, bright yellow powder.	"	53·38	3·2	"	"
3. . .	Soft, bright yellow powder.	"	52·89	3·5	"	"
4. . .	Soft, dull yellow powder.	"	54·26	5·56	"	"
5. . .	Soft, bright yellow powder.	"	53·81	5·21	"	"
6. .	Soft, bright yellow powder.	"	52·73	2·6	"	"
7. . .	Soft, bright yellow powder.	Amorphous and crystals	54·63	2·4	"	"
8. . .	Soft, bright yellow powder.	Amorphous.	53·37	3·6	"	"
9. . .	Soft, bright yellow powder.	"	53·84	4·25	"	"
10. . .	Soft, bright yellow powder.	"	53·72	2·91	"	"

The above data were obtained from samples collected in the Eastern United States, and represent the best manufacturers in this section. Dermatol is included. It is quite evident that the samples did not differ from one another very materially.

Nothing was removed by either alcohol or ether. All indicated the presence of nitrates with diphenylamine in a longer or shorter time. No arsenic was detected with Marsh's apparatus.

No. 7 contained many microscopical crystals. The process given by H. Causse[1] is said to yield a crystalline product. The method is, however, not suitable for practical purposes, and the writer is of the opinion that the above crystalline product was not obtained by this process. At all events, the amorphous is preferred, since it is less irritating to tender surfaces.

The reaction of bismuth subgallate on litmus paper appears to be anomalous. On treating this chemical with water, filtering and then ascertaining the reaction of the filtrate on litmus, it will generally be found neutral. But, if blue litmus paper be moistened and then laid on a small amount of the bismuth subgallate, it will be found that in a longer or shorter time an acid reaction will manifest itself.

The bismuth oxide was estimated[2] by ignition in a porcelain crucible and the reduced metal oxidized either by prolonged incineration or nitric acid or ammonium nitrate. It was found that prolonged heating gave results identical with those obtained by the use of either ammonium nitrate or nitric acid and with much less inconvenience. When nitric acid is used, great care must be exercised in evaporating all of the moisture before applying the burner, otherwise there will be loss by spirting, and in the cooling and reheating there is much danger in cracking the crucible. With ammonium nitrate there is less chance of loss by either spirting or breaking of crucible, but the writer much prefers to somewhat prolong the heating. With a little practice the operator can easily see when oxidation is complete.

The solubility of this bismuth salt in the fixed alkaline hydrates is a distinct advantage. Some claim that it is soluble in the alkaline carbonates also, but in this the writer has not been successful. There seems to be some solution, but not of such an extent as to be useful. Bismuth subtannate is also soluble in a 10 per cent.

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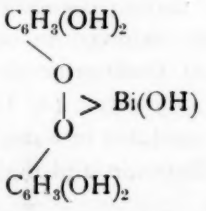
[1] 1893, *Comp. rend.*, *117*, 232; *Chem. Zlg.*, *17*, 216.

[2] Note—Since writing the above, Duyk (Bull. Acad. Med. Belg.) advises that the bismuth be estimated as an oxalate, since oxalic acid possesses the property of replacing all other acids in combination with bismuth. Bismuth oxalate (BiC_2H_4OH) theoretically contains 66·56 per cent. of bismuth, and it is claimed to be of quite constant composition, from whatsoever source obtained. Duyk advises the following procedure: Into a suitable vessel place about 1 gramme of the powdered substance, add from 30 to 40 centigrammes of oxalic acid, warm gently, add 100 c.c. of water, boil a few minutes and set aside. Collect the precipitate on a tared filter paper, wash with warm water and dry at 110° C.

solution of sodium hydrate, but very much more slowly than the bismuth subgallate. On heating, solution is much more rapidly effected, but this may be due to the hydrolising influence of the fixed alkali on the tannic acid, converting it into gallic acid. It must be stated, however, that one make of tannate is much more readily soluble than another. This may be due to a difference in the composition of the tannic acid employed.

The solubility of bismuth subgallate in sodium and potassium hydrate solutions is very striking and, naturally, the question is asked, why? On recalling to mind we find that bismuth subgallate is not the only bismuth compound, as commonly supposed, possessing this property; bismuth pyrogallate is just as readily soluble in the same alkaline solutions and otherwise possesses analogous properties. Bismuth subtannate was spoken of above. We have a similar phenomenon in the case of bismuth citrate and ammonium hydrate, in iron and ammonium citrate and many others.

There have been various chemical formulas assigned to this compound. H. Causse[1] found in his investigation that the salt lost two molecules of water, or 9 per cent., at 100° C., and assigns to it the formula $C_6H_2OHO_2CO_2Bi + 2H_2O$. He attributes the yellow color to the saturation of the phenol function of the acid. According to the above results, the bismuth subgallate supplied in this country is quite different from the article examined by Mr. Causse, for the highest amount of moisture obtained at 110° C. was only 5·56 per cent. Mr. Causse, however, probably worked with the crystalline article obtained by his process, yet the writer of this article also had one crystalline product, but its moisture was the lowest of any examined. There are some reasons for thinking that the yellow color may be due to the saturation of the phenol function, for instance, bismuth pyrogallate, whose formula is supposed to have the following configuration:



[1] 1893, *Comp. rend.*, *117*, 232; *Chem. Ztg.*, *17*, 276.

is yellow and readily soluble in the caustic solutions. But with phenol itself, bismuth forms a gray compound practically insoluble in sodium or potassium hydrate solutions.

The formula assigned by B. Fischer and B. Grützner is more nearly in accord with the results of this investigation. Their formula, $C_6H_2(OH)_3CO_2Bi(OH)_2 + H_2O$, requires the article to contain 54·23 per cent. of bismuth oxide; found in this investigation from 52·73 to 54·63 per cent. of bismuth oxide. This variation is due to different degrees of hydration.

Bismuth subgallate is a soft, light yellow, generally amorphous powder, of a somewhat variable composition (but may have some microscopic crystals), without odor or taste and permanent in the air; indifferent to light and may be sterilized at 100° C.; insoluble in water, alcohol, ether or dilute acids; soluble in solutions of the fixed alkalies and strong inorganic acids. When incinerated in a porcelain crucible the residue may vary from 53 to 55 per cent. Neither alcohol nor ether should remove anything. One gramme, calcined in a porcelain crucible and dissolved in dilute sulphuric acid, should not give any indication of arsenic with Marsh's apparatus.

TINCTURE OF FAT-FREE DIGITALIS.[1]

By Joseph W. England.

In 1892 I had the pleasure of presenting to this Association a paper on the subject of "Infusion of Digitalis." In discussing the chemistry of digitalis leaf, I stated then that the term digitalin had been given to a variety of products, but was generally reserved for the compound obtained by Schmiedeberg in 1875. The commercial digitalins, whether crystalline or amorphous, were stated to be varying mixtures of Schmiedeberg's digitalin, digitoxin, digitonin, digitalein, and certain decomposition products. Of these, all, save digitoxin, were believed to be glucosides. Including the decomposition products, these principles could be grouped into two classes, according to solubility. (1) Those soluble in alcohol, and insoluble or almost insoluble in water; (2) those soluble in both alcohol and water. Digitalin and digitoxin were assigned to the

[1] Read before the meeting of the Pennsylvania Pharmaceutical Association, held at the Philadelphia College of Pharmacy on June 14, 1899.

first class, and digitonin and digitalein to the second class; the tincture and fluid extract containing, most largely, digitalin and digitoxin, with some digitonin and digitalein, while the infusion contained digitonin and digitalein, with no digitalin or digitoxin. Hence the difference in clinical value between the aqueous and alcoholic preparations of digitalis leaves.

Reference was made to the superior therapeutic worth of the English leaves over the German, and this was ascribed to the fact that the English leaves were carefully freed from nerves and stalks (which had been shown to contain only one-fifth as much digitalin as the leaf parenchyma), thereby reducing the element of variability to a minimum. Since 1892, however, by personal advices received from London, the writer is convinced that much of the so-called English leaves are simply very carefully garbled German leaves, and not English cultivated leaves, as supposed.

Attention was also called to the fact that the freshly-made infusion was weakly acid in reaction, while the tincture gave the acid reaction more promptly, owing, probably, to a greater solubility of the acids of the leaf in alcohol, and the presence of a larger quantity in solution.

The acids present in digitalis leaves are the odorous antirrhinic acid of Morin (1845), and the fatty digitoleic acid of Kosmann, with which the digitaloic acid of Walz is probably identical. The percentage of fixed oil obtained was relatively high. By petroleum benzin exhaustion and spontaneous evaporation, I obtained, in 1887, about 5 per cent. The oil, or rather mixture, as there was evidently present both a volatile portion and a fixed oil, was a dark reddish brown liquid of a heavy persistently narcotic odor, largely soluble in alcohol, freely soluble in ether or chloroform, and not readily inflammable (showing the absence of traces of petroleum benzin). It left a permanently greasy stain on bibulous paper. Its specific gravity was about 0·850. Heated for eight hours it lost 5·4 per cent., and also lost its peculiar narcotic odor, becoming more fatty in character, indicating the loss of a volatile portion.

When tincture of digitalis is sometimes given, it causes profound gastric disturbance, even nausea and vomiting, and believing that, possibly, this might be due in part, if not wholly, to the fixed oil of the leaf and its free acids, the writer prepared, some years ago, a so-called fat-free tincture in which these two principles were eliminated.

Dr. Daniel E. Hughes, Chief Resident Physician of the Philadelphia Hospital, has kindly furnished me with the following clinical statement:

"For the past five years we have been using in the wards of the Philadelphia Hospital the tincture of fat-free digitalis made by Joseph W. England, the Chief Druggist of the hospital, to replace the official tincture. The vast majority of the cardiac and nephritic patients coming to the Philadelphia Hospital have had, as a marked and stubborn complication, chronic gastric catarrh, and could not stand the administration of the official digitalis tincture, but could take our more bulky infusion. To secure the desired cardiac and nephritic action of this valuable drug required large doses of the infusion, which was a very serious drawback to its use.

"Mr. England's attention was called to the subject, and he suggested that he might be able to prepare a tincture of digitalis of the same strength as the official preparation, but devoid of the nauseating proximate principles of the latter. He prepared his preparation and we submitted it to extended employment. After the continued use of this particular preparation of digitalis, I can speak of its efficiency and non-nauseating properties. I am confident that it is much more promptly absorbed than the official tincture, and this makes the cumulative action of this drug almost, if not altogether, *nil.* Again, its more prompt absorption is shown by its quicker action upon the heart and increase in the flow of the urine.

"The non-irritating properties of this special tincture of digitalis are forcibly shown upon its hypodermic use, abscesses having never followed its use, while the official tincture almost invariably causes pain, swelling and abscess-formation on hypodermic use."

This fat-free tincture of digitalis was made by exhausting the leaves, while freshly ground (to a No. 60 powder), with purified petroleum benzin, either by maceration with solvent in excess for forty-eight hours, if in small quantity, or by maceration and subsequent percolation, if in larger quantity, repeating the solvent treatment until all the fat, etc., is removed. The residue is then dried by exposure to air, taking care that no traces of benzin odor remain. While benzin is very volatile, the last portions of it volatilize rather slowly, relatively, when spontaneously evaporated, especially if adherent to vegetable structure. Exposure of the residue to the sunlight, as well as to open air, yields the best results.

After the benzin treatment the dried and powdered leaves are made into a tincture according to the process for the official product, 150 grammes of leaves being used to make 1,000 c.c., with diluted alcohol, with this difference, that the receiver is removed when the total percolate amounts to about 980 c.c, and it is then carefully neutralized with a sufficient quantity (about 10 or 15 c.c.) of the official 10 per cent. ammonia water, and the product is made to measure 1,000 c.c. with sufficient fresh percolate or diluted alcohol.

Or, with the usual weights and measures, 1,094 grains of the powdered leaves may be exhausted with diluted alcohol to yield 15½ fluidounces, and then about 1 or 2 fluiddrachms of 10 per cent. ammonia water will be required to effect neutralization, after which sufficient percolate, or diluted alcohol, should be added to make the whole product measure 1 pint. After standing for twenty-four hours the freshly-made tincture usually precipitates some coloring matters, etc., which should be removed by filtration through paper.

The product, as finally obtained, is a deep reddish brown, almost black liquid, keeping perfectly for years, of not unpleasant odor, and pure bitter taste. It has not the acrid odor or taste of the official tincture, and, unlike the latter, does not become turbid on admixture with water, but remains transparent with any amount of dilution.

The purposes of this procedure are two-fold: First, the benzin treatment removes the fat, and probably all the nauseating and odorous principles, and secondly, the ammonia treatment neutralizes the free acids present in the leaf, forming ammonium salts.

It does more than this. The neutralization with ammonia makes *all* the proximate principles in the tincture water-soluble, and not partly so as in the official product. (When the official tincture is diluted with water it precipitates.) This is especially valuable for the reason that all compounds before absorption by tissues must first be made soluble before they can be absorbed. By this means absorption is facilitated and assimilation is hastened, as will be shown by pharmacological results later.

When the fat-free tincture was first made, the desire was to obtain a preparation that would not nauseate, and clinical results in the Philadelphia Hospital have shown that this object has been very

generally accomplished. A short time ago, however, an even more valuable feature of the fat-free tincture became evident; this was the *rapidity* with which the preparation was absorbed and assimilated in comparison with the official product. Observations were then made to determine, clinically, the relative rapidity with which the fat-free tincture and the official tincture were each absorbed, noting (1) the time of primary effect; (2) the time of maximum effect, and (3) the pulse reduction or work, both in male and female patients, and both hypodermically and by mouth.

Through the kindness of Dr. F. A. Sherrer, formerly of this city (now of Hazleton, Pa.), this work has been done. The main difficulty was experienced in the selection of bed-cases in which, while the use of digitalis was indicated, the physical conditions were as nearly *uniform* as possible, so that comparative results could be had. The cases chosen were mostly rheumatic with endocarditis. In one or two cases there was arhythmia, which disappeared in fifteen minutes after the first dose. Patients were given the tinctures three hours after meals, when the stomach was practically empty. The fat-free tinctures one day, the official the next day. No food or water was taken during the time of administration. The beginning of each administration was so timed that there was no serious difference between the rate of pulse-beat when the giving of each preparation was commenced. At most, the primary difference was never more than six beats. It is obvious that if a heart is beating almost normally one day, when one tincture is given, and is beating tumultuously the next day when another tincture is used, that uniform conditions do not exist and comparative results cannot be had. The next essential is rest in bed, and perfect quiet.

Speaking of this in connection with digitalis administration, Dr. H. C. Wood writes (U. S. D., 1898, 478):

"Whilst the patient is in a horizontal position the pulse is very slow and strong, but when he rises to his feet it becomes at once rapid, irregular, small and feeble, and even hobbling."

Doubtless, sphygmographic tracings would have determined the results of *rapidity* of absorption and action more accurately, but as this means of observation was not available, it was not followed. A few preliminary trials made by the mouth showed that primary effects were had with the fat-free tincture in about fifteen minutes, and primary effects with the official tincture in about thirty minutes; so observations of pulse-beats were taken every fifteen minutes.

In those cases where there was tenderness after hypodermic injection and possibility of abscess-formation, this was aborted by local application of the following ointment:

Silver Nitrate	20 gr.
Sulphur, Sublimed	20 gr.
Ichthyol	1 dr.
Cerate	4 dr.
Hydrous Wool Fat	4 dr.

The samples of the tinctures used are submitted. They were both made from Allen's digitalis leaves; the fat-free tincture in January, 1898, the official in September, 1898. The following are the results obtained:

Case 1.—Male patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. March 29, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. March 30, 1899. Pulse.
90	3.45 P.M.	86
88	4.00 P.M.	86
88	4.15 P.M.	82
86	4.30 P.M.	82
84	4.45 P.M.	80
82	5.00 P.M.	80

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 75 minutes; pulse reduction or work, 8 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 60 minutes; pulse reduction or work, 6 beats.

Case 2.—Male patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. April 1, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. April 2, 1899. Pulse.
78	3.45 P.M.	80
74	4.00 P.M.	80
73	4.15 P.M.	78
72	4.30 P.M.	76
71	4.45 P.M.	73
71	5.00 P.M.	72

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 60 minutes; pulse reduction or work, 7 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 75 minutes; pulse reduction or work, 8 beats.

Case 3.—Male patient, tinctures given by *mouth*, doses 10 minims. Same patient as Case No. 1.

FAT-FREE TINCTURE. April 5, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. April 6, 1899. Pulse.
52	10.15 A.M.	52
49	10.30 A.M.	52
48	10.45 A.M.	50
48	11.00 A.M.	49
47	11.15 A.M.	48
47	11.30 A.M.	48
47	11.45 A.M.	47
48	12.00 M.	47
50	12.15 P.M.	50

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 60 minutes; pulse reduction or work, 5 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 90 minutes; pulse reduction or work, 5 beats.

Case 4.—Male patient, tinctures given by *mouth*, doses 10 minims. Same patient as Case No. 1.

FAT-FREE TINCTURE. April 6, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. April 7, 1899. Pulse.
76	3.30 P.M.	78
72	3.45 P.M.	78
70	4.00 P.M.	75
68	4.15 P.M.	74
70	4.30 P.M.	74
74	4.45 P.M.	72

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 8 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 75 minutes; pulse reduction or work, 6 beats.

Case 5.—Male patient, tinctures given by *mouth*, doses 10 minims. Same patient as Case No. 2.

FAT-FREE TINCTURE. April 8, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. April 9, 1899. Pulse.
60	9.00 A.M.	54
58	9.15 A.M.	54
57	9.30 A.M.	52
54	9.45 A.M.	50
54	10.00 A.M.	49
57	10.15 A.M.	49

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 6 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 60 minutes; pulse reduction or work, 5 beats.

Case 6.—Male patient, tinctures given *hypodermically*, 10-minim doses. Same patient as Case No. 2.

FAT-FREE TINCTURE. April 17, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. April 18, 1899. Pulse.
58	9.30 A.M.	54
54	9.45 A.M.	54
47	10.00 A.M.	50
46	10.15 A.M.	50
46	10.30 A.M.	49
48	10.45 A.M.	51
48	11.00 A.M.	52

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 12 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 60 minutes; pulse reduction or work, 5 beats.

Case 7.—Male patient, tinctures given *hypodermically*, doses 10 minims.

FAT-FREE TINCTURE. May 11, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 12, 1899. Pulse.
80	9.45 A.M.	80
78	10 00 A.M.	80
74	10.15 A.M.	78
70	10.30 A.M.	75
70	10.45 A.M.	74
70	11.00 A.M.	74
72	11.15 A.M.	76

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 10 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 60 minutes; pulse reduction or work, 6 beats.

Case 8.—Male patient, tinctures given *hypodermically*, doses 10 minims.

FAT-FREE TINCTURE. May 14, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 15, 1899. Pulse.
80	9.00 A.M., 9.45 A.M.	80
77	9.15 A.M., 10.00 A.M.	80
74	9.30 A.M., 10.15 A.M.	78
72	9.45 A.M., 10.30 A.M.	74
74	10.00 A.M., 10.45 A.M.	72
74	10.15 A.M., 11.00 A.M.	76
78	10.30 A.M.	—

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 8 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 60 minutes; pulse reduction or work, 8 beats.

Case 9.—Male patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 20, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 21, 1899. Pulse.
54	10.00 A.M., 9.15 A.M.	54
48	10.15 A.M., 9.30 A.M.	52
48	10.30 A.M., 9.45 A.M.	48
46	10.45 A.M., 10.00 A.M.	48
46	11.00 A.M., 10.15 A.M.	44 (asleep)
50	11.15 A.M., 10.30 A.M.	44
52	11.30 A.M., 10.45 A.M.	46

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction, 8 beats.

Official Tincture.—Primary effect in 15 minutes, full effect in 60 minutes; pulse reduction, 10 beats. This is the only case in which primary effect took place in 15 minutes with the official tincture, and as the patient was in an especially quiescent state preparatory to sleeping, the tincture had less work to do than usual, and did it more quickly. The marked reduction of pulse beats is due to the same cause.

Case 10.—Male patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 20, 1899. Pulse.	TIME.	OFFICIAL TINCTURE May 21, 1899. Pulse.
70	10.00 A.M., 9.30 A.M.	66
68	10.15 A.M., 9.45 A.M.	66
64	10.30 A.M., 10.00 A.M.	64
66	10.45 A.M., 10.15 A.M.	66
72	11.00 A.M., 10.30 A.M.	68

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 30 minutes; pulse reduction or work, 6 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 30 minutes; pulse reduction or work, 2 beats.

Case 11.—Female patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 21, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 22, 1899. Pulse.
67	9.30 A.M.	61
62	9.45 A.M.	62
70	10.00 A.M.	59
68	10.15 A.M.	66
68	10.30 A.M.	65
64	10.45 A.M.	60
60	11.00 A.M.	59
58	11.15 A.M.	52
70	11.30 A.M.	64

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 105 minutes; pulse reduction or work, 9 beats. The up-and-down character of these results shows that there must have been some disturbing factor introduced, such as disturbance of rest, etc., and the time required for full effect cannot fairly be considered.

Official Tincture.—Primary effect in 30 minutes, full effect in 105 minutes; pulse reduction or work, 9 beats.

Case 12.—Male patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 23, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 24, 1899. Pulse.
70	9.45 A.M.	68
66	10.00 A.M.	68
66	10.15 A.M.	64
64	10.30 A.M.	62
64	10.45 A.M.	60
68	11.00 A.M.	60

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 6 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 60 minutes; pulse reduction or work, 8 beats.

Case 13.—Male patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 23, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 24, 1899. Pulse.
72	9.45 A.M.	72
70	10.00 A.M.	72
64	10.15 A.M.	68
62	10.30 A.M.	66
64	10.45 A.M.	—

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 10 beats.

Official Tincture.—Primary effect in 30 minutes, full effect in 45 minutes; pulse reduction or work, 6 beats.

Case 14.—Female patient, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 25, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 24, 1899. Pulse.
67	9.30 A.M.	66
65	9.45 A.M.	66
66	10.00 A.M.	68
64	10.15 A.M.	64
64	10.30 A.M.	66
64	10.45 A.M.	64
64	11.00 A.M.	62
66	11.15 A.M.	60

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 45 minutes; pulse reduction or work, 3 beats.

Official Tincture.—Primary effect in 45 minutes, full effect in 105 minutes; pulse reduction or work from commencement, 6 beats.

Case 15.—Female patient, same patient as Case 14, tinctures given by *mouth*, doses 10 minims.

FAT-FREE TINCTURE. May 26, 1899. Pulse.	TIME.	OFFICIAL TINCTURE. May 27, 1899. Pulse.
68	10.00 A.M.	65
66	10.15 A.M.	65
63	10.30 A.M.	75
64	10.45 A.M.	61
60	11.00 A.M.	63
61	11.15 A.M.	63

Fat-Free Tincture.—Primary effect in 15 minutes, full effect in 60 minutes; pulse reduction or work, 8 beats.

Official Tincture.—Primary effect in 45 minutes, full effect in 45 minutes; pulse reduction or work from commencing pulse-beat, 4 beats.

SUMMARY OF RESULTS.

Case.	Fat-Free Tincture.			Official Tincture.		
	First Effect, Minutes.	Full Effect, Minutes.	Work or Beats Reduced.	First Effect, Minutes.	Full Effect, Minutes.	Work or Beats Reduced.
1	15	75	8	30	60	6
2	15	60	7	30	75	8
3	15	60	5	30	90	5
4	15	45	8	30	75	6
5	15	45	6	30	60	5
6 h.	15	45	12	30	60	5
7 h.	15	45	10	30	60	6
8 h.	15	45	8	30	60	8
9	15	45	8	15[1]	60	10
10	15	30	6	30	30	2
11	15	—	9	30	105	9
12	15	45	6	30	60	8
13	15	45	10	30	45	6
14	15	45	3	45	105	6
15	15	60	8	45	45	4
Averages . . .	15	49	7·6	31	66	6·4

h—hypodermic cases; others, by mouth.
[1] Exceptional case. Explained in text.

Twelve of the above patients were male and three female. In twelve of the cases the tinctures were given by the mouth, and in three, hypodermically, which latter are so marked.

From these results it may be said that, practically, the primary effects of the fat-free tincture were manifested in 15 minutes, and the maximum in 45 minutes; while, with the official tincture, primary effects were evidenced in 30 minutes, and the maximum in 60 minutes. In both cases, however, the *duration* of effect was the same—30 minutes. The pulse reduction, or work done, was slightly greater with the fat-free tincture than with the official. The most striking difference, however, exhibited between the fat-free tincture and the official tincture was the *much greater rapidity of absorption* and action of the former—showing a more speedy assimilation of the fat-free product. The time element of drug action is a very important matter in some cases, and might readily mean, with a

digitalis preparation, the difference between the life and death of a patient. No especial difference in the time of absorption between *hypodermic* injections and *mouth-administrations* was observable, but when the tincture was given hypodermically the pulse-reduction seems to have been greater with the fat-free tincture, though not extending over any greater length of time.

It would be unwise to draw too far-reaching conclusions from these results. Based, as they are, upon clinical conditions, and varying, as these do, with the personal factor in each case, they should be considered as approximate for the present, until supplemented by more extended work with the sphygmograph. At the same time, the remarkably concordant results gotten in the majority of cases, both with the fat-free tincture and the official, would seem to be fairly indicative of a number of conclusions.

RECENT LITERATURE RELATING TO PHARMACY.

ASSAY OF FLUID EXTRACT OF HYDRASTIS.

A new method of assay is suggested by N. Rusting (*Ph. Cent.*, 1898, 788). It consists of cooking 10 grammes of the fluid extract with 20 grammes water until the liquid is evaporated to 20 grammes, and filtration of the residue through infusorial earth or talc. Ten grammes of the filtrate is mixed with 25 c.c. ether and 3 c.c. ammonia water, and after shaking, 25 c.c. petroleum ether and 2 grammes tragacanth are added. Forty c.c. of the ethereal layer is then withdrawn and evaporated to 15 c.c., when the hydrastin crystallizes out, and is weighed. The tragacanth aids in the separation of the ethereal layer and the evaporation of 25 of the 40 c.c. of the ethereal liquid removed all the ether, leaving the petroleum ether, in which hydrastin is scarcely soluble. In fact, when the petroleum ether is separated from the crystals and evaporated, the residue is found to contain only canadine. Comparison of this method of assay with that of Linde (*Ph. Cent.*, 1895, 353), shows the two methods agree well with advantage in simplicity and quickness in favor of Rusting's process. H. V. ARNY.

A NEW METHOD FOR THE DETERMINATION OF THE MELTING-POINTS OF FATS.

Messrs. H. R. Le Sueur and A. W. Crossley, having experienced some difficulty in securing uniform results by the usual methods,

devised a very simple method that proved very satisfactory in their hands. The underlying principle of the method is that liquids show the phenomenon of capillarity, while solids do not. The melting-point is determined in the following manner (*see Fig. 1*): Into a thin-walled tube, *A*, closed at one end, place a fine capillary tube, *B*, open at both ends, then small particles of the substance under examination are placed into the outer tube, so that the lower end of the capillary tube is well surrounded by it. The whole is then attached to a thermometer by means of two rubber bands, *CC*, and then placed into a suitable medium, which is slowly heated and carefully stirred. The temperature at which the liquid is seen to rise in the capillary tube is taken as the melting-point of the fat. The usual precautions for taking melting-points must be observed.—1898, *Jour. Soc. Chem. Ind.*, *17*, 988. L. F. KEBLER.

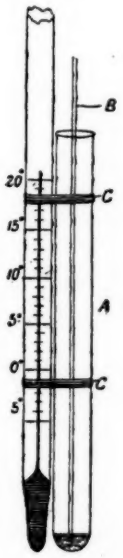


FIG. 1.

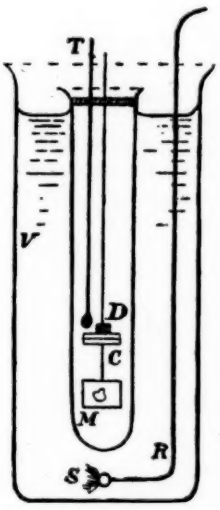


FIG. 2.

APPARATUS FOR DETERMINING MELTING-POINTS.

L. N. Vandevyver, 1898, *Ann. Chim. anal. appl.*, *13*, 397; from *Jour. Soc. Chem. Ind.*, 1899, *18*, 298. (*Fig. 2.*)

In this apparatus a wire rod is provided with a mirror, *M*, fixed at an angle of 135°, and two rings, one, *C*, which is fixed, and the other, *D*, which is movable. Between these two rings is clamped

a piece of filter-paper, on which is placed a particle of the substance to be examined. The rod, with its appendages, and a delicate thermometer, are then fixed in a test-tube by means of a cork, as shown in accompanying cut. The whole is then placed into a beaker, *V*, containing water, glycerine or paraffin, in which is a stirrer, *R*, provided with a brush to remove adhering bubbles. The whole is then carefully heated, and the melting-point determined by observing the reflection by the mirror of the stain produced on the paper by the substance, on melting. A dull glass disk is to replace the paper, if a substance produces a stain at the ordinary temperatures. For material having high melting-points, the glass mirror can be replaced by a metallic one. L. F. K.

EDITORIAL.

PENNSYLVANIA PHARMACEUTICAL ASSOCIATION.

It has been customary in the July issue of this JOURNAL to devote considerable space to the proceedings of the Pennsylvania Pharmaceutical Association. Inasmuch as the meeting this year was held in the city of Philadelphia, which has been referred to as "the Birthplace of Liberty," and in the Philadelphia College of Pharmacy, which has been considered to be "the cradle of American pharmacy," we gladly devote a little more than usual attention in these pages to the transactions of this meeting. There were many commendable features of this meeting, as will be seen on reading the report of the proceedings in another part of this JOURNAL. The President's address, like that of his predecessor, may be said to have been devoted to a sound and judicious consideration of the problems concerning the practical and commercial side of pharmacy to-day.

The reports of the various committees, particularly that of the Chairman of the Committee on Legislation, indicated that strong efforts are being made to ameliorate the existing conditions in regard to product patents. The N. A. R. D. received much encouragement on every hand. The officers of this organization must realize their great responsibilities, and that they received much encouragement from the various organizations, pharmaceutical press and other avenues of influence. It is to be hoped that all their future actions will be, as the President suggested, as wise and conservative as they have been in the past.

There were an unusually large number of good papers presented, quite a number of which are printed in this issue of this JOURNAL. The Entertainment Committee, while it did not contribute any papers or reports, did a most important work, which required a great amount of time and special ability, in providing for the comfort of the members, and it may be said, to a certain extent, the fuel which enabled so much work to be done so easily. The work of the Association and its pleasures were admirably divided, and the adage that "There is a time to play and a time to work" was well adhered to, so that the amount of business transacted in two days was unusually great, and the amount of pleasure realized during the remaining time was more than usual.

REVIEWS AND BIBLIOGRAPHICAL NOTICES.

FORMULAIRE DES MÉDICAMENTS NOUVEAUX POUR 1899. Par H. Bocquillon-Limousin. Introduction par le Dr. Huchard. 1 vol. in-18 de 324 pages, cartonné. 3 francs.

This formulary of the new medicaments is a valuable addition to this subject. Besides the consideration of a large number of plants recommended by therapeutists, there will be found a consideration of nearly all the recently introduced chemicals, etc.

Among these may be mentioned: Benzeucaine, Captol, Céarine, Cosaprine, Créosolide, Eigone, Erythrol, Euphtalumine, Gaïacyl, Glycéro-phosphate de quinine, Guaïaquine, Guéthol, Hydrargyrol, Ingestol, Iodamylum, Iodocaséine, Iodogallicine, Iodoterpine, Largine, Oléates alcaloïdiques et métalliques, Orthophosphate d'argent, Oxoles, Phosphate de bismuth, Protargol, Quinochloral, Saligallol, Salicylate de mercure dissimulé, Saliformine, Satitannol, Styrone, Tannone, Thiocol, Ursal, Valerydine, Validol, Vanadine.

Of all the medicines treated there are given the synonyms, description, physical and therapeutical properties, mode of administration and dose. The work has been scientifically and accurately done, and is to be recommended as an important addition to the literature of newer remedies.

THREE THOUSAND QUESTIONS ON MEDICAL SUBJECTS, ARRANGED FOR SELF-EXAMINATION.—With the proper references to standard works in which the correct replies will be found. Second Edition, enlarged. Philadelphia: P. Blakiston's Son & Co., 1012 Walnut Street.

The ideas are excellent ones, and the questions are well gotten up. The only unfortunate thing is that the "Standard works in which correct replies will be found" are, in fourteen out of the sixteen books of reference mentioned, all Quiz Compends. It would have been well if some of the standard works other than "Quiz Compends" were referred to.

DRS. HARVEY AND DAVIDSON'S SYLLABUS OF MATERIA MEDICA.—Revised in accordance with the "British Pharmacopœia," 1898. By William Martindale. Tenth edition. London: H. K. Lewis, 136 Gower Street, W. C. 1898.

This little book of sixty-four pages was originally prepared for the use of the medical students in the University of Aberdeen. It seems to be employed by medical students as a guide in their studies of the more important articles and preparations in the B. P.

PENNSYLVANIA PHARMACEUTICAL ASSOCIATION.

The twenty-second annual meeting of the Pennsylvania Pharmaceutical Association convened at the Philadelphia College of Pharmacy on Tuesday morning, June 13th, 1899, at 10 o'clock, with the President, Mahlon N. Kline, in the chair. The Association was welcomed on behalf of the city of Philadelphia by Mayor Ashbridge, who, in a very pleasant address, referred to the fact that the first salary he ever received was in the wholesale drug house of Robert Shoemaker & Co., of this city, and that he remembered those days of service as among the most pleasant in his life. The President then called upon Mr. J. H. Redsecker, who responded in a very happy manner. The next in order was the reception of delegates from the neighboring State pharmaceutical and allied associations, which were well represented. The general tenor of the

remarks of these representatives indicated a fraternal spirit, and a hopeful view of the satisfactory solution of the problems with which the pharmaceutical world was confronted. In behalf of the Association Prof. J. P. Remington, in responding to the greetings of the delegates, said that he felt it an honor to reply to them, and that the occasion was a unique one in that he had never seen so much time devoted to the speeches of delegates. Then on behalf of the College he welcomed the visitors and delegates, and called attention to the portraits of former professors and others, whose silent faces looked down upon them, and who would also welcome them if they were present. The President then gave his address, which we consider of such importance that we reproduce it nearly in full. It is as follows:

I find, in looking over the President's address delivered last year, that he commenced the same with an expression of profound thankfulness to a kind Providence for having spared the lives of so many of our members and permitting them to meet again in annual session. While I feel that I should repeat this expression in behalf of our members, I desire especially to do so for ex-President Remington and myself, for the almost miraculous deliverance from danger to which we were but recently exposed during the frightful railroad accident which occurred on the 12th of May, at Exeter. I venture to say for Professor Remington, and will say for myself, that I feel this deliverance to indicate that our lives were spared for some wise purpose, and as an evidence that there remains some important work yet to be done, and I ask Divine guidance in the performance of whatever duty may be allotted to us.

It has been customary, and is eminently fitting, that at each annual meeting some note be taken of the progress in the pharmaceutical world. Gathered, as we are, for this twenty-second annual meeting of our Association in the rooms of the Philadelphia College of Pharmacy (an institution which, through its instructors, has been instrumental in equipping a larger number of young men to take their places in the pharmaceutical world than any other similar institution in the country), it would be proper that considerable attention should be given in this address to the scientific interests of the pharmacist's calling. I regret that I am not able to do this, but express the hope that those of our members who have gone out into the pharmaceutical world from this time-honored institution may contribute at this meeting, in one way or another, through papers or discussions, to the sum of our pharmaceutical knowledge, and make up what must necessarily be lacking in my contribution to the proceedings.

When you did me the honor to elect me President a year ago, I take it that it was done for the purpose of having an address which would deal more largely than is usual with the business interests of the druggists' calling. As is well known, I have in years past given considerable attention to the trade problems which the retail, as well as the wholesale, druggists of this country have sought to solve, having occupied for ten years the position of Chairman of the Committee of Proprietary Articles of the N. W. D. A. I would, therefore, scarcely be discharging my duty if I did not devote some attention to the present status of the retail druggists' trade interests. When I look over the report submitted at the last meeting, and find that but about 350 of the upwards of 3,200 druggists of this State are members in good standing in this Association, I am reminded that there is the utmost necessity of our bestirring ourselves to find the reason

why this Association (the foremost, I think, in most respects of any of the State associations) should not be able to attract to its ranks more than 10 per cent. of the whole.

It is true that we have had for several years a Committee on Trade Interests. It does not appear to me, however, that the druggists of this State have felt that this Committee has fully met their expectations, or that the Association has made itself sufficiently valuable to them to induce them to become members. While, according to our Constitution, the aim of this Association is "to unite the educated and reputable pharmacists and druggists of the State, to improve the science and art of pharmacy, and to restrict the dispensing and sale of medicines to regularly educated druggists and apothecaries," and this has generally been construed to mean that our deliberations are to be largely scientific, the latter portion of the above quotation from Article II of the Constitution certainly warrants us in assuming that "restricting the sale of medicines to regularly educated druggists" is a part of our work. Believing that the word "medicines" here was not intended to refer only to those dispensed upon physicians' prescriptions, but to apply also to ready packeted remedies known as "patent medicines," I felt warranted, when the call for a meeting of those interested in the formation of a National Association of Retailers to act upon trade matters was promulgated, and I was asked, as President of the Pennsylvania Pharmaceutical Association, to appoint delegates from this Association, to comply with the request. I consulted with our Secretary and the Chairman of the Executive Committee, and as a result appointed the following delegates: Charles L. Hay, of Dubois; J. H. Redsecker, of Lebanon; Wm. McIntyre, of Philadelphia; A. J. Kaercher, of Allegheny.

Messrs. Redsecker and McIntyre were unfortunately unable to attend this meeting, but Messrs Hay and Kaercher were present and rendered valuable aid in the formation of the National Association. Mr. Hay was made the Chairman of the Committee on Trade-Marks and Patents and Mr. Kaercher, Chairman of the Auditing Committee. Under what favorable auspices this Association was launched at its meeting in October last, and what it has since accomplished, has been so fully brought to your notice through the columns of the pharmaceutical press that it is useless to refer to it here in detail.

I venture, however, to express the opinion that many of the errors made by former similar organizations formed during the last fifteen years were carefully and wisely avoided by this. It was at once seen that if anything of value was to result from the efforts which were to be made by this new and latest organization, it must come as the result of co-operation between the manufacturer, the wholesaler and the retailer. Acting upon this conviction, a brief platform was adopted on which all three classes could unite, and as the three organizations representing these three classes were then in session simultaneously in the city of St. Louis, the endorsement of each was secured before adjournment. The application of the principles laid down in this platform and the work of the Association was committed to an able executive committee and a most efficient Secretary, Mr. Thos. V. Wooten, with headquarters in the city of Chicago. Membership of each State and local association was made up of delegates, each local and State association being entitled to one delegate for each 100 active members or fraction thereof. It was stipulated that "such delegates shall be actively engaged in the retail drug business." It was recog-

nized that the immediate regulation of prices of proprietary medicines was not to be insisted upon, but that local organizations should be encouraged to get together with a view of effecting some change in the margins on such articles, and that as large a proportion of the retail druggists of this country as could be interested should be united under this N. A. R. D. banner, and an amelioration of the trade conditions be effected whenever, wherever and however possible.

The next meeting of this Association is to be held in Cincinnati, on October 3d, 4th, 5th and 6th of this year. We are requested by the Executive Committee, through the Secretary, to officially endorse the purposes of this Association, to provide for a representation through delegates at this next meeting, and to contribute by an assessment of 25 cents upon each of our active members for the purpose of helping the N. A. R. D. put into execution the plans formulated at their last convention, or such as may be agreed upon at the coming convention. I suggest that these requests be referred to our Committee on Trade Interests, and that they be asked to bring before us for our action resolutions placing our Association in line with this request.

Whether the assessments shall be upon the basis outlined in the request is a question which that Committee, owing to the condition of our finances, must carefully consider.

We must acknowledge that that which our Committee on Trade Interests has been unable to do for the druggists we may hope to accomplish more effectually by co-operating with this national body. If, at its next meeting, the deliberation of the National Association be as wise and conservative as the action of its Executive Committee has been hitherto, I am free to say that I have the strongest confidence in their success in many of their undertakings.

One of the questions which has been agitating our neighbors in New York State and City has been the question of shorter hours for drug clerks. As this is a question which may confront the members of our own Association in the near future, I have thought proper to refer to it in this address.

No amendments or alterations to the Pharmacy Law were proposed during the last session of Legislature, though several recommendations were made by the President in his last annual address (who was again made a member of the Committee on Legislation), and though the Association, at the last meeting, endorsed the general Pharmacy Law sent to us for our approval by a Committee of the American Pharmaceutical Association. I would like, however, to reiterate the importance of at least one amendment recommended by my predecessor. Sufficient time has now elapsed since this law has been in effect to show the importance of its being amended, in this one important particular, namely, that after the expiration of a limited time, say two years from the date of its passage, every applicant for a proprietor's certificate should be required, when appearing before the Pharmaceutical Examining Board, to have a diploma from some accredited college of pharmacy. Nothing is clearer than that a sufficient number of young men are willing and able to thoroughly equip themselves for the responsible position of compounding the prescriptions of physicians, through pharmaceutical education, to fully supply the needs of our growing population, to warrant this recommendation.

It was wisely provided, when this law was first passed, that those then in business, whether having a pharmaceutical education or not, should not be dis-

turbed. It was also provided that at that time at least the college of pharmacy diploma requirement should not be incorporated in the bill; but, as already stated, it is admitted by all who opposed such a proviso at that time that now the time has come when this change should be made.

It is urged, I know, by some that, owing to the unprofitableness of the drug business, no further or greater restrictions should be imposed upon those engaged therein, but it should not be forgotten that those who are most successful in this calling to-day are those who are best equipped, through thorough pharmaceutical education, and as the medical examiner's bill fully recognizes this principle, and thus furnishes direct encouragement for the better education of those who are to be admitted to the practice of medicine in this State, so surely should we recognize the importance of encouraging thorough pharmaceutical education in our pharmaceutical colleges.

The Committee on Legislation will doubtless report upon the effort which was made to amend our Poison Law, by the passage of a bill restricting the sale of opium and its preparations, and cocaine, to those presenting physician's prescription, and prohibiting the putting up of such a prescription one week after it had been written. It was urged, by those supporting this legislation, that opium and its preparations were sold and administered freely to minors and others by unscrupulous persons, and that thus great injury was being done, both physically and morally, especially to the young, in some sections of this State.

Those who supported this measure seemed to us to overlook the fact that, while it may be true (and unfortunately I believe is true) that here and there a druggist can be found who so far forgets his moral obligations as to sell freely to any one opium and its preparations, cocaine, etc., to those who are known by the seller to purchase them for immoral purposes, there is equal danger of physicians being found here and there who would be quite as likely to forget their moral obligations and write prescriptions indiscriminately, so that the evil would not be corrected, while great hardship would be inflicted upon the very large proportion of conscientious pharmacists, who would, under this bill, if it had become a law, have been obliged to refrain from selling even a dose of paregoric until the customer had first obtained a physician's prescription. While the bill did not receive favorable consideration at the hands either of the House or the Senate, it emphasized to our Committee the importance of having some well-digested and carefully drawn Poison Law prepared for the next session of the Legislature, and this was promised by them.

The efficient work which was performed by the Chairman of the Committee on Legislation, in the effort of securing a correction of the patent laws under which our friends in Germany now can, and do, compel us to pay tribute to the chemists of that country, without in any way reciprocating the favor, will doubtless be brought before you at this session. I can only say that we have been fortunate in securing for the Chairmanship of this Committee a man who has most intelligently considered the true interests of our members and the druggists generally in this direction, and was accorded the honor of an extended and attentive hearing on November 21, 1898, before the Commissioners on the Revision of our Patent and Trade-mark Laws, appointed by President McKinley.

One of the anomalous conditions to which attention has been called through

the discussions before these Commissioners is that, while the German chemists are able to levy this tax upon us in this country, they have no protection at home, and, what is still worse, considering the matter of our reciprocal relations, a citizen of this country who attempts to market a product in Germany, but who has failed to secure trade-mark registration from the German Government, may be prohibited, in some cases has been prohibited from selling his own product in that country, if someone there has been shrewd enough to anticipate him in securing the registration of a trade-mark upon something under a similar name, in anticipation of the application being made by the owner of the same in this country.

The National Pure Food and Drug Law is still pending in Congress. A second meeting of the Pure Food and Drug Congress was called in the city of Washington, on January 18th last. Our Association was represented by ex-President Redsecker and a number of others of our members, who found, when they reached Washington, that the enterprising Secretary of the Congress had elaborated a programme which certainly had the appearance of being controlled more largely by a desire to keep those who were delegates in the city of Washington for three or four days, than to specially further the interests of this bill. Many addresses were down on the programme, some of them worth listening to, but most of them devoted to rehashing what the delegates already knew and had previously endorsed, and no material changes were recommended in the bill pending, and no material aid, so far as the delegates from this Association could tell, was given to the work in hand. The coming session of the U. S. Congress will doubtless consider this bill, and it is not improbable that it will secure favorable passage.

We should see to it that no attempts are made to jeopardize the interests of the pharmacists in this proposed legislation, which we believe, as the bill now stands, are fairly well taken care of.

The imposition of the Stamp Tax upon medicines, in which we have special interest, was noted in the last annual address, and its provisions, as outlined therein, went into effect on the first day of July last, and became an additional burden upon the retail druggist, not only to the extent of compelling him to stamp his stock on hand, but of increasing the cost, to an extent even greater than the Revenue Tax imposed, by the makers of many proprietary remedies. It was probably to this cause, more than any other, that we owe the formation of the N. A. R. D., and one of the first and most notable triumphs of that organization was the correction, to a considerable extent, of what seemed an especially unnecessary and uncalled-for imposition of a new burden threatened from some quarters.

The effort to advance margins at retail was, however, hoped to largely reimburse the retail dealer for this change in prices. While in some localities this was successful, it is to be regretted that in many others, notably in the larger cities, it was not. This latter condition, I believe, is largely due to the fact that many makers of proprietary medicines sell direct at largest discounts to those able to buy the quantities for retailing, who usually are the aggressive cutters, and who, by reason of this advantage, are able to sell a single package for the price paid by their less fortunate competitors, the average retail druggists.

Among the wisest steps taken by the N. A. R. D. was the stand they took against this position of manufacturers, and it is gratifying to note that, in a

bulletin recently issued by the Secretary of this Association, it is stated that fully 75 per cent. have recognized the justice of their demand that this be discontinued. Congress, at its last session, did not consider any changes in this internal revenue law. As time goes on, however, it is believed that some amendments which seem to be needed will be made to the law to correct some inequalities, though it is not believed that an abolition of this internal revenue tax will be brought about for many years to come; in fact, it is the general consensus of opinion that internal revenue taxes will be a fixed part of our fiscal policy, the same as it has been for many years in England.

The Executive Committee will refer to the deaths which have occurred in our ranks during the past year. I cannot close this address, however, without referring to the death of one who is so sadly missed at this meeting. While he had reached an age where it was but natural to expect that we could not hope to have his genial presence with us many more years, yet none of us could think of our late fellow-member and first President of this organization, Mr. Chas. A. Heinitsh, as an old man.

It will be remembered that in connection with the presentation of the medal which the members of this Association presented to him a year ago, in commemoration of the fiftieth anniversary of his entrance into pharmacy, I related the incident told by Bishop Potter. We little dreamt that this was as prophetic as it was fitting.

We have the consolation, in lamenting his departure, to feel that we *did* make known to him on that occasion, in a way that brought the tears of appreciation to his eyes, our appreciation of his worth, and that we made known to him, in no uncertain terms, our loving regard *before*, not after, his departure hence. It may truly be said that he was a benediction amongst us while he lived, and that his memory will be revered so long as this Association exists.

REPORTS OF OFFICERS AND COMMITTEES.

The Secretary, Dr. Miller, of Harrisburg, said that his report was much the same as during previous years. The Treasurer, Mr. Lemberger, reported a balance of $269.86. Charles L. Hay, Chairman of the Executive Committee, reported the election of a larger number of new members than usual during the year, and of the participation of the delegates of the Association in the organization of the N. A. R. D., at St. Louis. In his report on Trade Interests, J. H. Knouse considered the present effort to remedy the cut-rate evil on proprietary articles, and said that the Pennsylvania Association are asked to become members of the N. A. R. D. and endorse what they have done in regard to requiring manufacturers to sell at jobbing rates only to legitimate and approved wholesalers. He further said, however, that this will have little or no beneficial effect in re-establishing list prices, unless both manufacturer and jobber are required to absolutely refuse supplies to any one not maintaining full retail prices. The Chairman of the Committee on Legislation, W. L. Cliffe, reported as follows:

"According to instructions received at the last session (see Report for 1889, p. 29), your committee, late in June, 1898, arranged to secure the legal opinion upon the status of the *Phenacetin Cases*, for which an appropriation was made. After a careful study of the question undertaken, for the purpose of keeping the expense within the amount appropriated and presenting a clear and lucid

array of facts for the judicial action of the lawyers, it was decided to call in a chemical expert, and Prof. Samuel P. Sadtler was selected on account of his familiarity with the subject. His report is a clear and comprehensive chronology of the nitro-phenols and their derivations which yield phenacetin and its congeners. His report was then placed in the hands of the law firm of Fraley & Paul, of Philadelphia, who reported upon it to your committee. A copy of both reports in printed form is hereby appended. In view of the fact that the cases involved in this cause are still going through the various legal steps towards a definite judicial decision, it makes *ex parti* comment unnecessary at this juncture.

"*Revision of Trade-Mark and Patent Laws.*—At a meeting in New York, on November 21, 1898, of the Commission * appointed by President McKinley for the purpose of reviewing the patent and trade-mark laws and reporting to Congress the changes deemed necessary, your Chairman was invited to be present.

"The argument by him was that the present laws admitted the raiding of the pockets of the people of these United States by foreign chemical manufacturers of immense sums, and figures were submitted showing the difference in prices of the same substances of identical sources of manufacture in Canada, Germany and the United States.

"The opposition to these views was represented by Mr. Dickerson, of New York, whose argument clearly showed that he was unfamiliar with the broad principles of equity and justice to the people of this country, upon which the opposition by pharmacists generally to the existing order of things is based. A short quotation from the printed brief shows clearly the spirit which permeates every line of it; it is the sum of his argument: 'The shallows murmur while the deeps are dumb.' 'It is not the strong and responsible houses or associations that are so anxious to have the law changed, but it is, as a rule, the cut-rate man, the man who sells adulterated drugs, the man who cares not for the purity of his chemicals.' The absurdity of this is apparent on its face, as the very man described by Mr. Dickerson is reaping a harvest from the sale of Canadian or German phenacetin at United States prices, and the 'strong and responsible houses and associations' hesitate about committing any act which can be construed as wrong-doing. It is thus pretty clearly indicated why the 'strong and responsible houses and associations' want to see this question settled.

"*House Bill No. 153.*—On February 16th, of this year, there was introduced into the House of Representatives a bill, the title of which was: 'An act to regulate the sale and use of opium, its derivations and all preparations of which opium or any of its alkaloids is a constituent part; cocaine or any preparation thereof, and to prevent the injurious use of the same.' A similar bill was introduced into the Senate at the same date. The bill was drawn by a lawyer, of York, Pa., for a law and order society in that place. According to their story, a most deplorable condition of affairs existed in that hitherto virtuous town; boys in knickerbockers were rapidly becoming addicted to the hypodermic injection of morphine and cocaine; it was a sort of mania that had become fixed. Your committee, with the aid of the officers of the Association,

* Francis Forbes, A. P. Greely, Judge Peter Grosscup.

first tried to have the bill dropped on account of some preliminary work that had been done on a new poison bill, in which they thought it was probable that the wishes of the friends of House Bill No. 153 could be met. As it was impossible to draw a bill of this class without careful study of every detail, it would not have been possible to have it ready to present at the last session; this proposition did not meet with agreement from the friends of the measure, as they claimed that the conditions existing in York needed prompt legislative treatment. Your committee then submitted the following as an amendment of the original bill. (See this JOURNAL, April, 1899.)

"The matter finally dragged along until the close of the session, and the bill was referred and re-referred, until it was not acted upon through the lack of time. Your committee specially wish to refer to the intelligent aid given by two members of the House, Mr. E. H. Fahey, of Philadelphia, and Mr. Wm. C. Nisbet, of Pittsburg, who are both pharmacists."

Charles L. Hay, Chairman of the delegation to the convention at St. Louis, at which was organized the National Association of Retail Druggists, made a report on the causes leading up to this step and the progress of the new organization.

Immediately following this report, the Committee on Recommendations in the President's Address made its report, which was adopted *seriatim* and as a whole.

The report of the Committee on Adulterations was read by Prof. F. X. Moerk in the absence of Professor Emanuel, Chairman, which dealt principally with individual cases of errors in prescription work. The President, Mahlon N. Kline, said that he was disappointed in the usual reports of the Committee on Adulteration, dealing, as they do, with minor mistakes in prescriptions, whereas a large amount of adulteration is going on in competition with legitimate houses.

In connection with the Committee on Adulterations, Mr. Kebler reported some recent adulterants met by him in the course of his work.

On examining some vanillin recently, he came across a sample that had a melting point of 77° C., and upon further examination it was found to consist of 6 per cent. of vanillin and 94 per cent. of acetyl iso-eugenol, so broken as to resemble vanillin; the direct antecedent of vanillin. More recently there has come to his notice vanillin that consisted of about 90 per cent. of benzoic acid and 10 per cent. of vanillin, and was informed that this article is quite largely used in the manufacture of vanilla extract, a sample of which was shown. Another sample of vanillin sent in was nothing but simple coumarin.

He also has met with a double fluoride of potassium and antimony that could be employed as an adulterant of tartar emetic to advantage, and the present requirements of the Pharmacopœia would not indicate it at all, not even in estimating the amount of antimony present, because the double salt of potassium antimony fluoride could be so made that the percentage of antimony would be identical with that contained in tartar emetic.

He also reported that ferrous oxalate would form a dangerous substitute as an adulterant of bismuth subgallate, from the fact that it has a color identical with that of the article just mentioned.

The Committee on Chemistry recommended that the Association take action on the nomenclature to be adopted by the next U. S. Pharmacopœia, especially in connection with the halogen alkaloidal salts.

PAPERS AND QUERIES.

The presentation of reports was interspersed with the reading of papers, which served to maintain the interest throughout the business sessions. They were as follows:

WOOD TAR CREOSOTE.

By Lyman F. Kebler.

The author gave a communication which was of considerable interest, and said that formerly the popular opinion appeared to be that creosote was simply a mixture of guaiacol and creosol, of which the former predominates in some cases, and the latter in others, but the demand for the salts of guaiacol recently have made such inroads upon guaiacol, that in place of finding creosote containing as high as 60 per cent. of guaiacol to-day, it is very difficult to find an article containing as much as 20 per cent. of guaiacol.

According to his results it would appear that the commercial creosote was almost entirely devoid of guaiacol. The per cent. varied from none to sixteen. According to his experiments the author is of the opinion that creosote has never contained as much as 60 per cent. of guaiacol. This is evidenced by not only his work, but also by the work of A. Béhal and E. Choay, who found that the fraction obtained by distilling crude wood tar creosote between 200 and 210° C. contained at the most only about 25 per cent. He also suggested that the requirements in the boiling of the Pharmacopœia be extended so that they would range between 200° and 220° C., instead of the present range of boiling point, since it is evident that guaiacol comes over boiling 205° C. There were also quite a number of methods given for distinguishing between the genuine creosote and the spurious articles.

THE ASSAY OF BELLADONNA LEAVES.

By Frank X. Moerk.

This paper is printed in full (see page 320, of this JOURNAL). In the discussion which followed, Mr. Kebler said that he heard the paper with considerable interest, but that he did not entirely agree with the author, and that he considered the method of percolation, as described by the author, as too cumbersome and too lengthy for practical application with a large number of assays. Professor Moerk called attention to the fact that by his method uniformly higher results were obtained, and that the discrepancies of Keller's method were overcome by the time required in this process.

ODOR AS AN AID IN THE RECOGNITION OF DRUGS.

By Clement B. Lowe.

The author has endeavored to work out a classification of drugs based on their odors, though on account of the personal element involved no two investigators will probably agree to all of the conclusions reached. The bulk of the paper was taken up with a proposed classification of drugs according to their characteristic odor.

William C. Alpers, of New York, thought that the scientific method of classifying odors of drugs would be to trace them to the chemical compounds which produce these odors. He said that in the Pharmacopœia the term "characteristic" is frequently used, which indicates that we do not know what the odor is.

He also spoke of the term aromatic as being applied to a large number of organic compounds, and that, therefore, the term did not mean much.

ARTIFICIAL FOODS.

By J. Percy Remington.

This paper will appear in a later issue of this JOURNAL. Mr. Kebler, in commenting upon this paper, said that he carried out experiments which showed that infants four months old are capable of digesting starch. Among others taking part in the discussion of this paper were Professor Lowe, Messrs. Lemberger and Stedem.

ESTIMATION OF CODEINE.

By Henry C. C. Maisch.

The author takes 0·300 gramme of codeine and places it in an Erlenmeyer flask with about 20 c.c. of water. To the flask is attached, by means of a closely-fitting soft rubber stopper, a delivery tube, of the following construction: The portion connected with the flask has an internal diameter of about $\frac{3}{16}$ inch. About 4 inches above the stopper the tube is bent at right angles, and 6 inches from this it is bent again, so as to bring this portion parallel with the first. This limb is about 4 inches long, and is fused to a tube having a ½-inch bore, and is about 18 inches long. The lower end of this is drawn out to a bore of about ⅛ inch, and is then bent upward. This tube is used without a condenser. The end of the delivery tube dips into 20 c.c. decinormal hydrochloric acid diluted with sufficient water, so that the orifice is about ¼ inch below the surface of the liquid. After the apparatus is set up, add 10 c.c. of a 10 per cent. solution of ammonium chloride to the flask containing the codeine, and this is at once attached to the tube. The flask is now heated and the liquid kept in a state of ebullition until about one-half has distilled over. The acid liquid is allowed to cool. The delivery tube is then washed out with water and the washings added to the acid solution. This is now titrated with decinormal KOH solution, using coralline or rosolic acid as an indicator; 316·31 grammes of codeine ($C_{18}H_{21}NO_3 + H_2O$) or 298·35 grammes anhydrous codeine are equivalent to 36·37 grammes of absolute hydrochloric acid. From this we have 1 c.c. of decinormal HCl representing 0·031631 gramme of hydrated codeine or 0·029835 gramme of anhydrous codeine.

Among those who discussed this paper were Mr. Kebler and Professor Moerk.

SOME NOTES ON CHONDRUS.

By Henry Kraemer.

The author considered some of the morphological characters of this plant, and referred particularly to its remarkable mode of reproduction, which appears to be that of a triple conjugation. He also considered the collection of the drug on the Massachusetts coast, and advanced some reasons for modifying the definition of the U.S.P.

TINCTURE OF FAT-FREE DIGITALIS.

By Joseph W. England.

This paper appears on page 332 of this JOURNAL. Those remarking upon this paper were Professor Lowe and Mr. Eppstein.

LABORATORY NOTES.

By Charles H. La Wall and Robert C. Pursel.

This paper contains the records of some of the various drug products examined by the authors during the year, and shows, in a measure, the quality of the goods upon the market. Mr. Procter thought the information presented by Messrs. La Wall and Pursel was very valuable.

BISMUTH SUBGALLATE.

By Lyman F. Kebler.

This paper is printed in full in this Journal (see page 326).

HOW FAR CAN COLUMBIAN SPIRITS REPLACE ALCOHOL IN MANUFACTURING BY PHARMACISTS?

By D. J. Thomas.

The author considers the use of Columbian spirit limited in pharmacy, and thought that it might be employed in making tincture iodine, tincture arnica and soap liniment. It is a ready and rapid solvent for corrosive sublimate, and may therefore be substituted in the preparation of "bed-bug poison." It may be used in preparing embalming fluids, burning in spirit lamps, under chafing-dishes, also in the manufacture of the most delicate aniline colors, dissolving shellac, gums and resins for varnishes, for cleaning plate-glass, jewelry and metals. Columbian spirit is used in the manufacture of oil of wintergreen synthetically. It is also employed in the preparation of bay rum, Florida water and various other toilet waters.

In discussing this paper, Dr. J. T. Rodman, of Hawley, said that it would not do in some sections to use wood alcohol to prepare tincture of arnica, because some Germans were in the habit of taking the tincture internally. Prof. F. G. Ryan said that he had come across a full line of fluid extracts for internal use made with Columbian spirits, or wood alcohol. Professor Remington said that one phase of the subject not touched upon was that the Pharmacopœia did not recognize the spirit named, or wood alcohol, and druggists that used it were liable to get into trouble, as the law in some States recognizes the Pharmacopœia as an authority. He also referred to the difference in solvent action of methyl and ethyl alcohol, and advised pharmacists to go slowly in using wood alcohol for making pharmacopœial preparations.

Among others taking part in the discussion were Messrs. Eppstein, Boring and Kebler.

IS THE DEMAND FOR TABLET TRITURATES ON THE DECLINE?

By D. J. Thomas.

In 1894 a single operative manufactured 25,000 tablet triturates daily. With improved apparatus, the daily output per operative is, on an average, 100,000, or an increase of four times as many. In 1894 the compressing machines then in general vogue yielded a daily output of about 35,000 tablets; with new rotating machines many times that number can be manufactured by each machine per day. After years of observation, the writer is of the opinion that tablets have come to stay, and advises the pharmacist making his store a physician's supply depot.

THE AMUSING SIDE OF PHARMACY.

By J. H. Redsecker.

In this paper the author referred to some of the queer and ludicrous orders that he had received during his long business career. One of these, over which he had puzzled a long time before he solved it, was for "I. E. Die," which was construed finally to mean tincture of iodine. The President then called upon Dr. William Harris, of Hamburg, Pa., who also contributed very much to the amusement of the occasion.

SOME PARTIALLY UNEXPLORED FIELDS FOR OCCUPATION OF THE IDLE HOURS OF THE PHARMACIST.

By F. W. E. Stedem.

The author urged the pharmacist to confine himself to that work for which, by education and precept, he is best suited.

THE MODERN PHARMACIST.

By John F. Patton.

The author gave some reflections anent the commercial side of pharmacy. Among other things, he said that he believed that pharmacy affords as fair a field with as much promise of success for man's endeavor as any other occupation. To an inquiring mind it is a vista of unlimited extent. From the commercial side no one can complain of the lack of variety of nature products with which it deals. The druggist must be a good business man as well as a skillful pharmacist. The author believes in advertising in the daily newspaper; that success or failure depends alone upon the individual, and that nothing is so conducive to making a man successful as conferences with his fellows, such as are to be had at the annual pharmaceutical association meetings.

THE MEDICAL DRUGGIST.

By Louis Emanuel, Ph.G.

The writer claims that there seems to be no justification for doctors to handle drugs and such medicines which properly belong to the drug store in direct competition to legally qualified druggists.

MISCELLANEOUS BUSINESS.

A special committee having been appointed by the President to frame resolutions on the death of Charles A. Heinitsh and Prof. Henry Trimble, the following resolutions were read by the Chairman, Professor Remington, and adopted:

MR. CHARLES A. HEINITSH.

Whereas, Through an all-wise Providence, the Pennsylvania Pharmaceutical Association has suffered inexpressible loss through the death of our first President and staunch friend, Mr. Charles A. Heinitsh, of Lancaster, Pa., who has been taken to his eternal home in the fullness of years and after a life of long and useful service; be it therefore

Resolved, That in the loss of one who has endeared himself to every member by his rare qualities, his nobility of character and his sterling virtues, we bow in submission to His will, and we have had an example set before us that it should be our greatest aim to emulate.

Resolved, That this Association place upon its records this tribute to the memory of one whose kindly heart and loving spirit, though absent from our

counsels, can never be forgotten by any of his associates who have enjoyed his companionship and friendly advice.

Resolved, That this Association convey to his deeply attached wife and companion for many years, our sincere sympathy in her affliction and our assurance, as we mingle our tears with those of his many friends, that we are comforted by the belief that he is enjoying the full fruition of the hope and faith that he so frequently expressed of a blessed Immortality.

PROFESSOR HENRY TRIMBLE.

WHEREAS, The Pennsylvania Pharmaceutical Association, during the past year, has lost, by the death of Prof. Henry Trimble, one of its most earnest and valuable members; and be it

Resolved, That we hereby record upon our minutes our high appreciation of his labors in our behalf; his willingness to serve this body in any capacity, but particularly in the special field of his activity, chemical science, is gratefully recognized.

Resolved, That this Association convey to his widow our heartfelt sympathy in her bereavement, and that a copy of these reolutions be sent to her.

J. H. Redsecker, as Chairman of the Nominating Committee, presented the following report, which was unanimously adopted: President, Charles Newton Boyd, Butler; First Vice-President, Charles Lamar Hay, DuBois; Second Vice-President, Dr. Charles A. Weidemann, Philadelphia; Treasurer, Joseph Lyon Lemberger, Lebanon; Secretary, Dr. Jacob Augustus Miller, Harrisburg; Executive Committee, Daniel Judson Thomas, Scranton; Sigmund W. Heinitsh, Lancaster; Cyrus Jacoby, Bethlehem; Local Secretary, Charles H. Marcy, of Altoona.

John F. Patton, the Chairman of the Committee on Time and Place of Next Meeting, reported that the Committee had unanimously agreed upon "Maple Park Springs, Ebensburg, Cambria County," as the place, and June 19, 1900, as the time for the next annual meeting.

SOCIAL FEATURES.

The social features of the meeting were unusually attractive and enjoyable. The President's reception was held on Monday evening, June 12, in the Philadelphia College of Pharmacy. The visiting members and delegates were thereby afforded an excellent opportunity of becoming acquainted and meeting each other before the regular business sessions. On Tuesday evening there was an excursion to Willow Grove Park, when refreshments were served at the Casino, and an excellent musical programme rendered by the celebrated Banda Rossa. On Wednesday evening there was a reception and dance given by Philadelphians to the visitors, in the Assembly Room of the Union League. The remaining days, Thursday and Friday, were spent in pleasurable pursuits at Atlantic City.

PROFESSOR JOSEPH P. REMINGTON has recently had conferred upon him, by Northwestern University, *honoris causa*, the degree of Doctor of Pharmacy.

FRANK X. MOERK, heretofore Instructor in Chemistry, has been elected to the chair of Analytical Chemistry in the Philadelphia College of Pharmacy, made vacant by the death of Professor Henry Trimble.